Southern Medical Journal

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SEPTEMBER 1956

VOLUME 49 NUMBER 9

Southern Medical Journal

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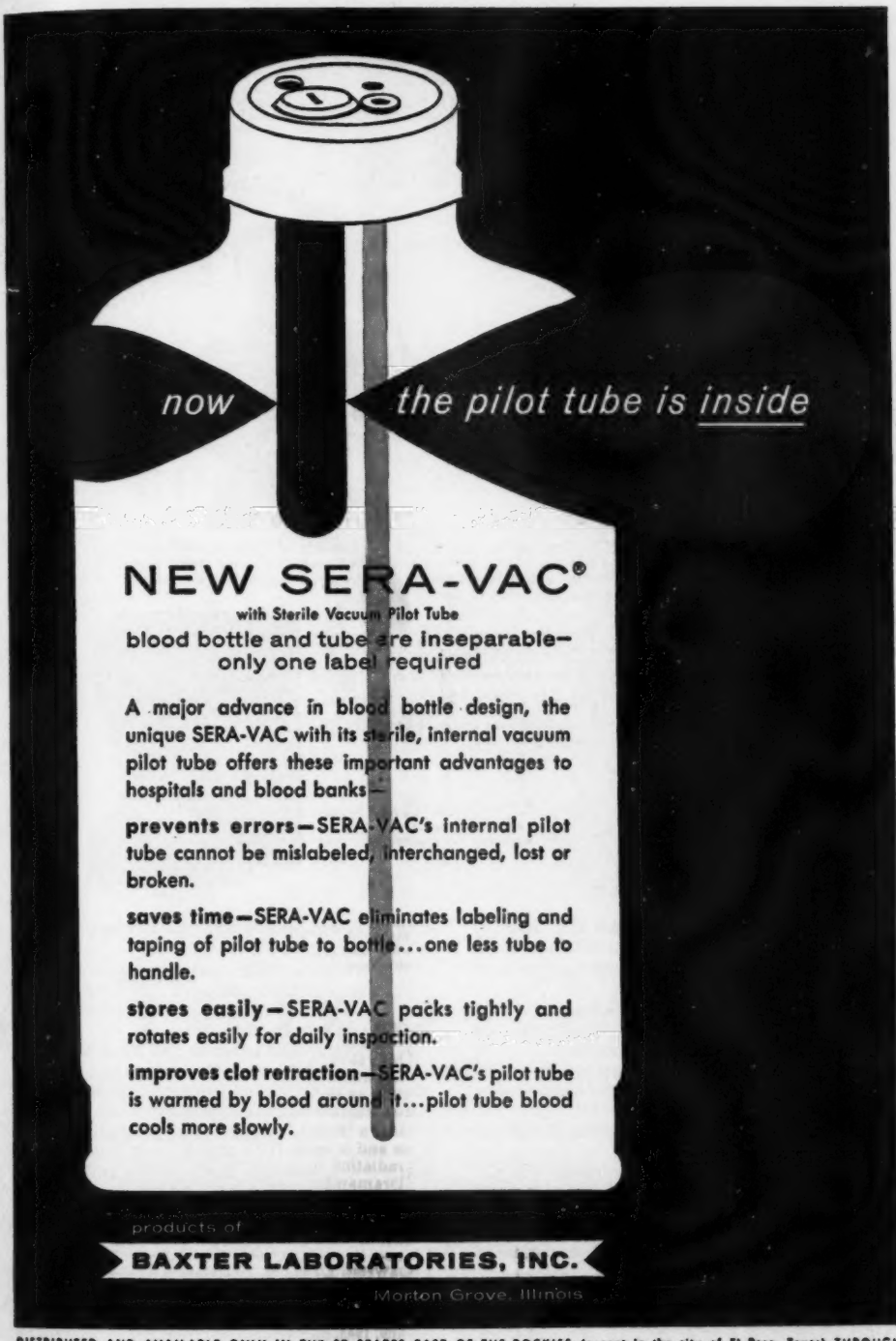
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2. Fluctuating subtotal hearing loss, usually affecting the higher tones, is noted at the same time as vertigo.
3. Tinnitus, usually unilateral, is associated with the deafness and dizziness.

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1. DeWeese, D. D.: Symposium: Medical Management of Dizziness. The Importance of Accurate Diagnosis, Tr. Am. Acad. Ophth. *58*:694 (Sept.-Oct.) 1954.
2. Jackson, C., and Jackson, C. L. (editors): Diseases of the Nose, Throat, and Ear, Philadelphia, W. B. Saunders Company, 1945, pp. 368; 414.
3. Queries and Minor Notes: Ménière's Syndrome, J.A.M.A., *141*:500 (Oct. 15) 1949.

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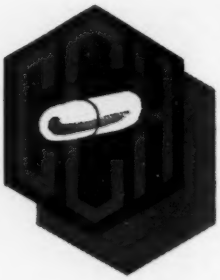

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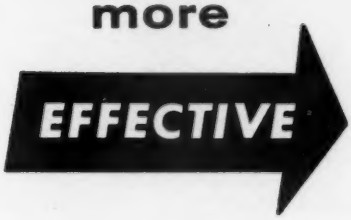

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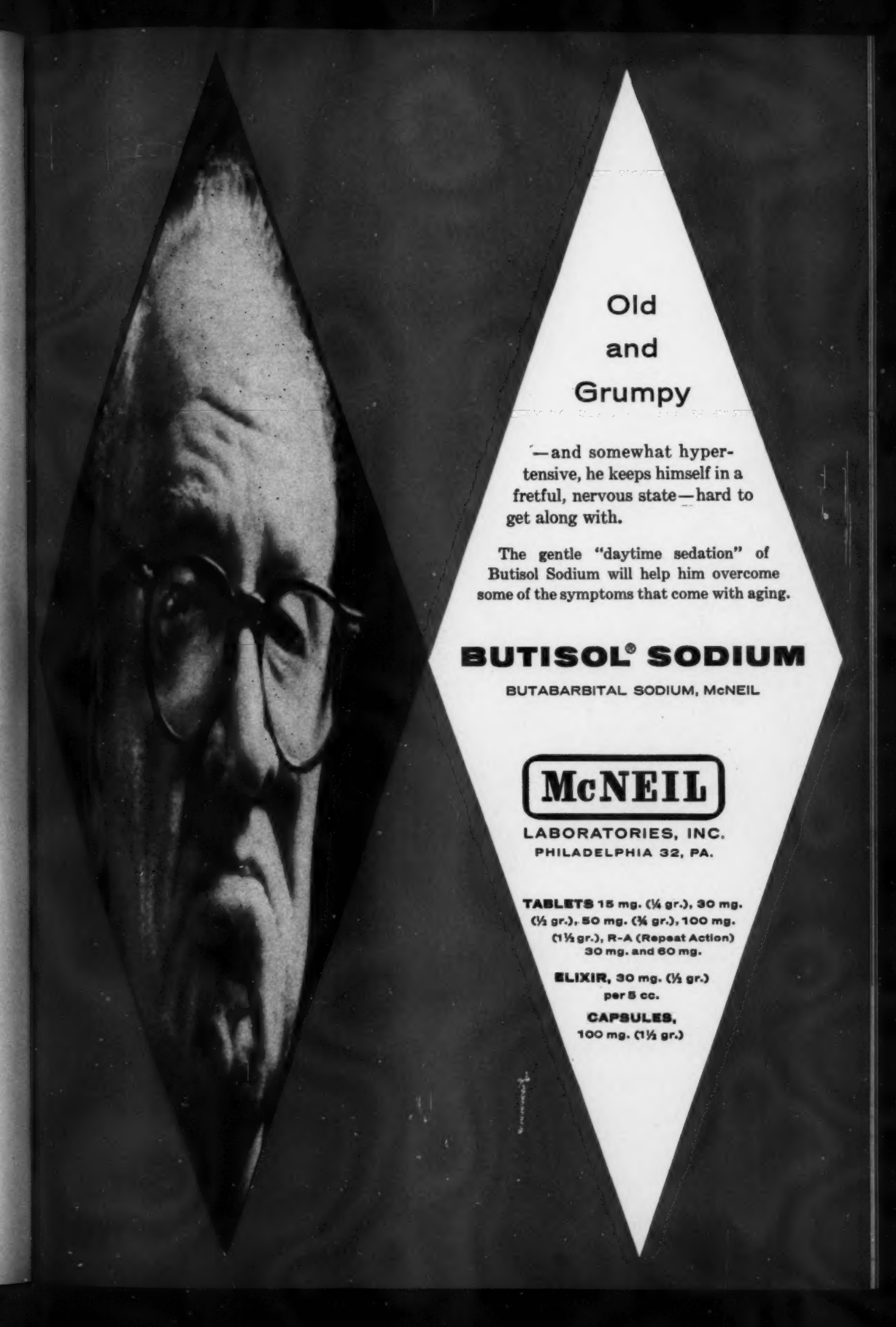
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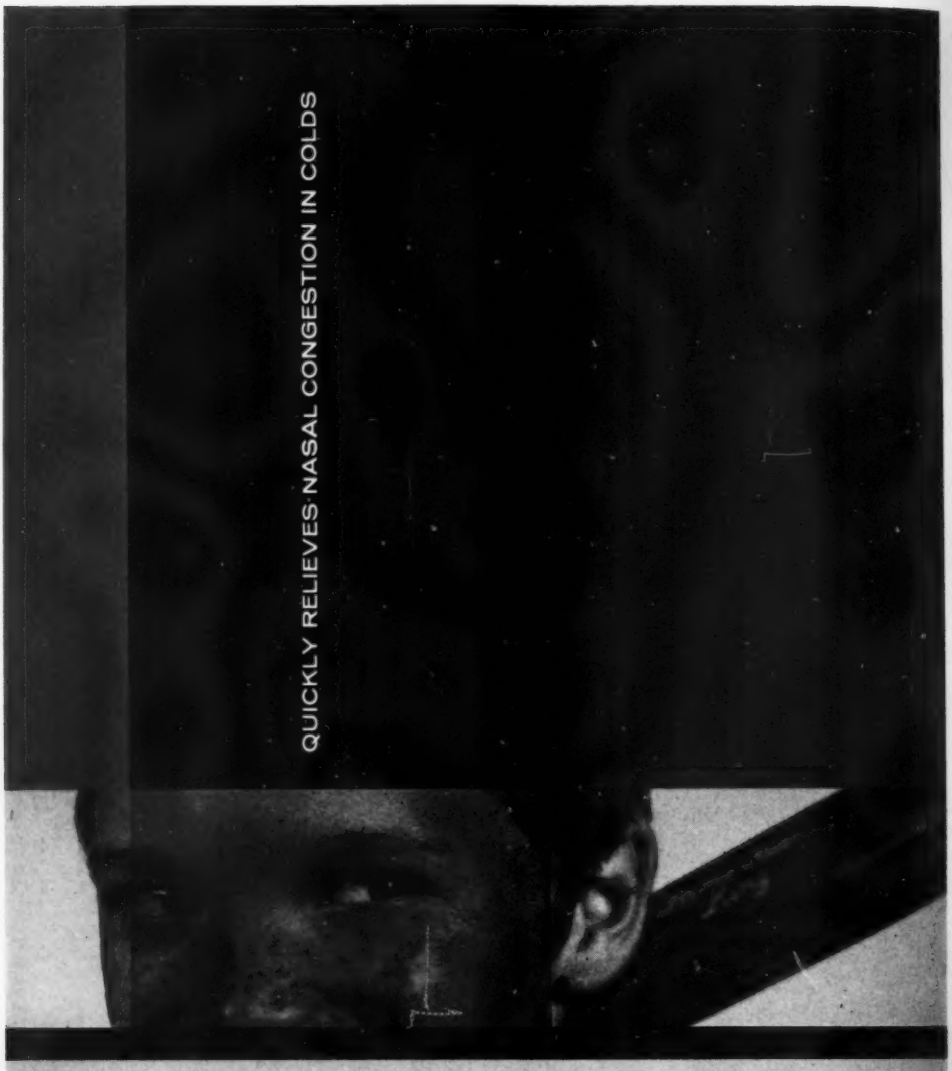

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1. Benaron, H.B.W., et al.: Am. J. Obst. & Gynec. 69:776 (Apr.) 1955

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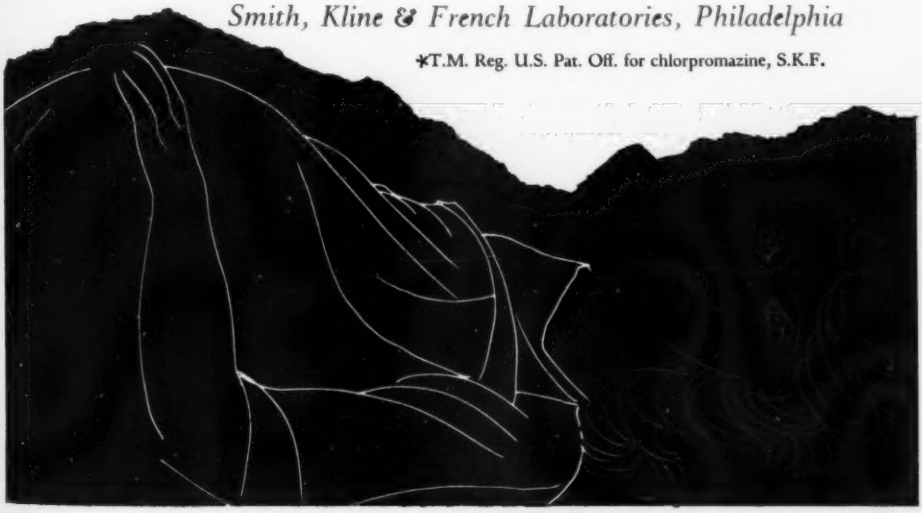

Erythromycin in the treatment of osteomyelitis

8/3/55

CASE SUMMARY

On 6/2/55, patient, male, age 28, fell on an old fracture and refractured the middle third of the right femur, superimposed on an old osteomyelitis.

On 7/7/55, the wound was saucerized and a hemolytic S. aureus (coag. +) was isolated from the osteomyelitis. Disc sensitivities were: penicillin, 10 units; erythromycin, 10 mcg.; tetracycline, 10 mcg.

On 7/15, the patient was placed on erythromycin therapy 400 mgm. q. 6. h. Patient afebrile after erythromycin started. X-rays showed evidence of healing with callus formation. No septicemia and clinical evidence indicates control of the infection.

On 8/3, the cast was removed and leg recast. Wound was in good condition with minimal drainage.

Diagnosis: fracture middle third of right femur, complicated by osteomyelitis.

Result: erythromycin aided healing of the old osteomyelitis and kept the infection under control.

*Communication to Abbott Laboratories

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HOW OLD IS OLD?

"The really old people are those 10 years older than myself."[1]

"In the lay mind, anyone past 60 is ready for the discard . . ."[2]

". . . there are only three principal phases in the span of life: infancy, adolescence and senescence."[3]

"One finds alert, interesting, active folks in the 80's and, on the other hand, there are people in the 20's and 30's who have all the characteristics of old age."[4]

THE REAL QUESTION

To the physician on the firing line of daily practice, the question of "how old is old?" seems academic. To him, a more valid question is "How can I allay the effects of the aging process?"

FIVE PROBLEMS IN AGING

The answer, according to most authorities, is manifold, for five treatable problems seem to predominate. One, obviously, is gonadal hormone decline. Another is mild anemia. A third is the decreased production of gastric and digestive enzymes. Mineral-vitamin deficiency is the fourth. And the fifth – perhaps most important – is inadequate high-quality protein intake.

THERAPY FOR AGING

Judging from this confused clinical picture of aging, therapy for the problem would appear difficult. However, most physicians agree that a product which could correct most or all of these five commonest problems would remove past obstacles to satisfactory response. Such a product would, essentially, be true "preventive geriatrics."

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* Protein deficiency among the aging apparently stems from their excessive intake of white-flour foods which furnish incomplete protein of low biologic value. White bread protein, for example, has been shown by nutrition studies in animals[5] to be deficient only in the amino acid, lysine. In human subjects metabolic determinations indicate that the addition of supplemental lysine to a basal white-flour protein diet can convert a negative nitrogen balance into a positive one.[6]

A WORD ABOUT SYMPTOMATOLOGY

In spite of jokes to the contrary, the patient who states in the professional office that "old age is creeping up" is a rare bird indeed.

Seldom is old age the presenting complaint. Thus the physician, after correcting the specific complaints, must re-evaluate the whole person to judge his candidacy for "preventive geriatrics."

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Molybdenum (from Sodium Molybdate)	2 mg.
Copper (from Cupric Sulfate)	1 mg.
Manganese (from Manganous Sulfate)	1 mg.
Magnesium (from Magnesium Sulfate)	6 mg.
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**Enzymatically active defatted material obtained from 1,500 mg. whole fresh liver and stomach.
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l-Thyroxine	0.1 mg.
Ethinyl Estradiol	1 mcg.
Methyltestosterone	1 mg.
Liver Fraction I	25 mg.
Ethyl Alcohol	0.5 cc.

Dosage: One teaspoonful twice daily before meals, or as required.
Supplied: In 16 fluid ounce bottles, prescription only.

Bibliography

1. Anonymous. 2. Rosenthal, P.: Geriatrics 10:382 (August) 1955. 3. Lansing, A. I.: Symposium on Problems of Gerontology, National Symposium Series No. 9 (August) 1954. 4. Mason-Hohl, E.: Quoted in W. Va. Med. J. 51:16 (January) 1955. 5. Rosenberg, H. R., et al.: Arch. Biochem. and Biophys. 49:263, 1954. 6. Bricker, M., Mitchell, H. H. and Kinsman, G. M.: J. Nutrition 30:269, 1945. 7. Masters, W. H. and Ballew, J. W.: Geriatrics 10:1, 1 (January) 1955.

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1. Kramer, P.: Med. Clin. North America, 39:1381, Sept. 1955.
2. Morrison, Samuel: Am. J. Gastroenterology 22:309 (1954).
3. Rossett, N. E., Rice, M. L., Jr., Gastroenterology 26:490 (1954).

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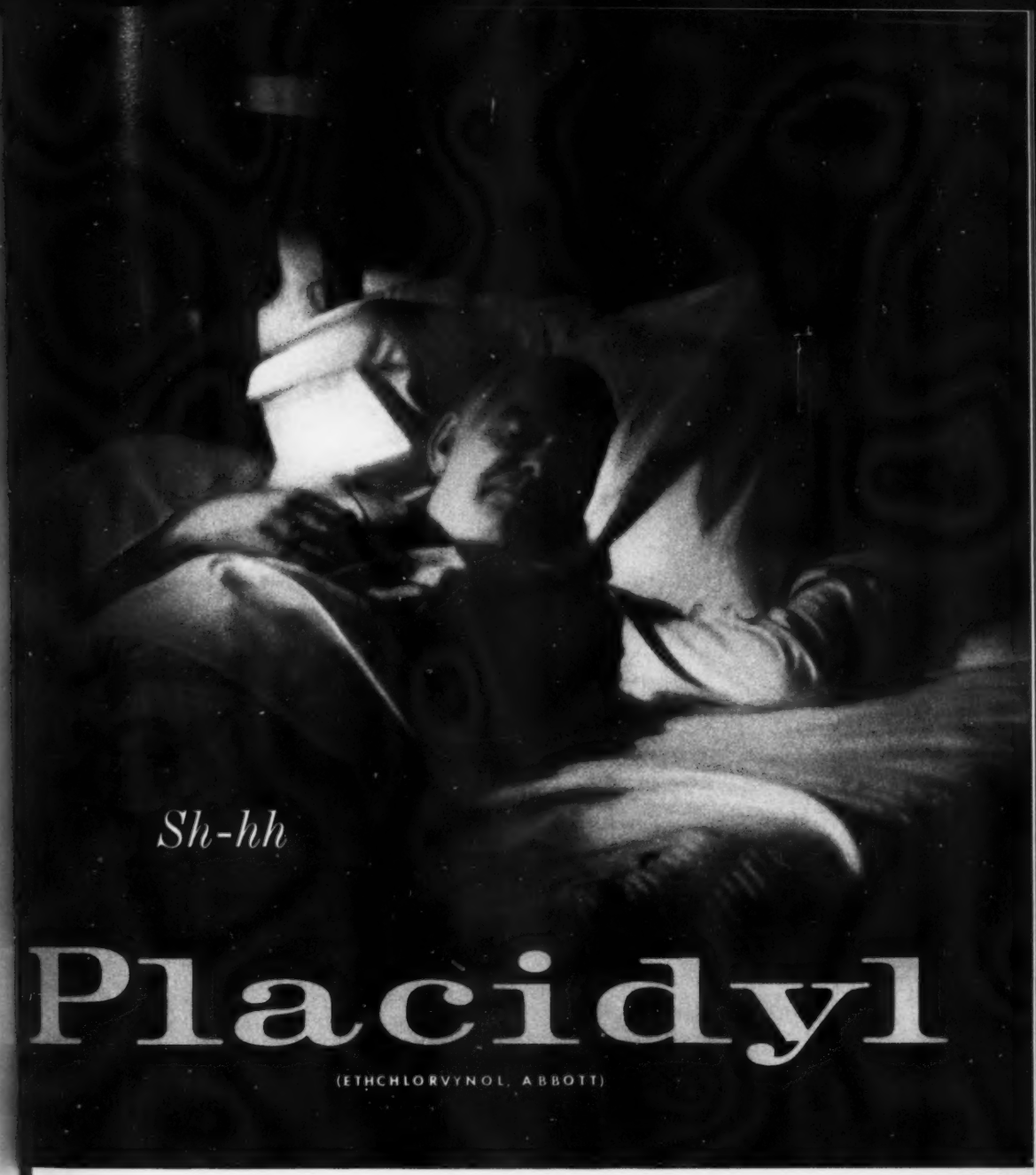

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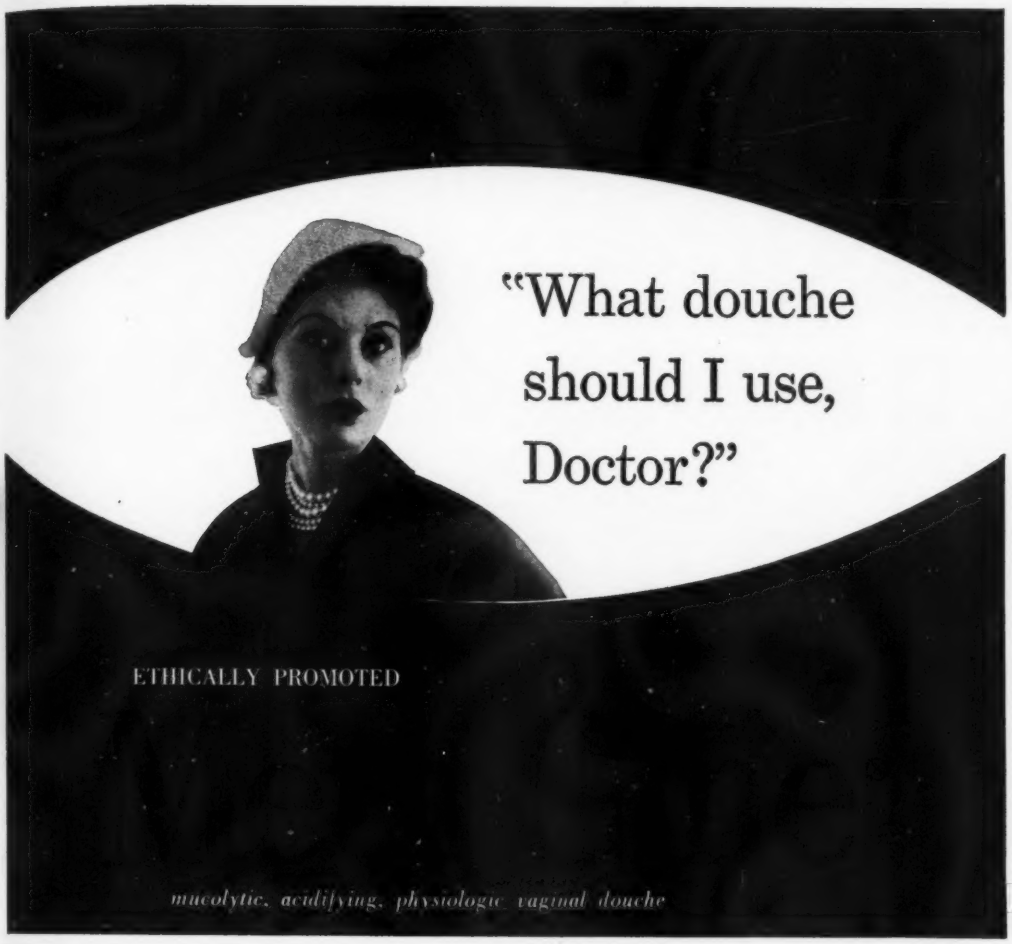

In answer to questions about douching you can recommend META CINE with complete confidence BECAUSE META CINE:

1. is a safe, soothing douche (pH 3.5) containing methyl salicylate, eucalyptol, menthol, chlorothymol and PAPAIN to liquefy mucus. CITRIC ACID to help restore the proper acid pH, discourage pathogenic organism, promote normal vaginal flora. LACTOSE to feed the physiologic Doderlein bacilli.

2. is pleasant and refreshing to the patient . . . and deodorizing.

3. has a surface tension of 56 dynes/cm as compared to 72 dynes/cm for the usual vinegar douche.

4. is economical . . . only two teaspoonfuls to two quarts of water . . . supplied in eight-ounce containers.

5. is useful as a routine, cleansing douche, as an adjuvant when treating leukorrheal infections, and following cervical cauterizations and conizations.

UPON YOUR REQUEST *a free supply of instruction sheets will be sent for your convenience in advising patients on the correct douching technique.*

BRAYTEN PHARMACEUTICAL COMPANY, 3810 St. Elmo Avenue, Chattanooga 9, Tennessee

In Congestive Heart Failure
R_x 'Wide Safety Margin'
GITALIGIN®

WHITE'S BRAND OF AMORPHOUS GITALIN

Authoritative investigators have reported that the digitalizing dose of Gitaligin is approximately one-third the toxic dose.[1-5]

This "wide margin of safety" (difference between therapeutic and toxic doses) permits rapid digitalization and successful maintenance with a minimum of toxic side reactions—even in refractory cases where other glycosides have failed.[6] And, cost to your patient is no greater than ordinary digitalis preparations.

Supplied: Scored tablets of 0.5 mg. Bottles of 30 and 100.

References: 1. Ehrlich, J. C.: Arizona Med. *12:* 239 (June) 1955. 2. Weiss, A., and Steigmann, F.: Am. J. M. Sc. *227:* 188 (Feb.) 1954. 3. Dimitroff, S. P.; Griffith, G. C.; Thorner, M. C., and Walker, J.: Ann. Int. Med. *39:* 1189 (Dec.) 1953. 4. Hejtmancik, M. R., and Herrmann, G. R.: Texas St. J. M. *51:* 238 (May) 1955. 5. Batterman, R. C.; DeGraff, A. C., and Rose, O. A.: Circulation *5:* 201 (Feb.) 1952. 6. Denham, R. M.: J. Kentucky St. M. Assoc. *53:* 209 (Mar.) 1955.

It's so easy to switch to wide safety margin Gitaligin. Follow these simple dosage equivalents wherever digitalis therapy is indicated

DIGITALIS PREPARATION	AVERAGE DAILY MAINTENANCE DOSE	GITALIGIN DOSAGE EQUIVALENT (APPROX.)
Digitalis leaf	0.1 Gm.	0.5 mg.
Digitoxin	0.1 mg.	0.5 mg.
Digoxin	0.5 mg.	0.5 mg.

WHITE LABORATORIES, INC. Kenilworth, N. J.

TANGIBLE RELIEF IN PREMENSTRUAL TENSION

another indication for Diamox*

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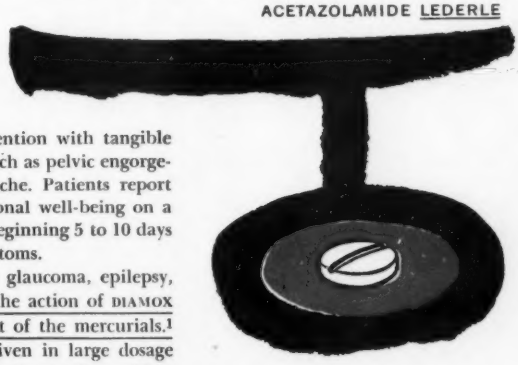

A single tablet of DIAMOX controls fluid retention with tangible relief of symptoms of premenstrual tension such as pelvic engorgement, tightness of skin, pruritus and headache. Patients report marked improvement of physical and emotional well-being on a simple regimen of DIAMOX: one tablet daily, beginning 5 to 10 days before menstruation, or at the onset of symptoms.

Of proven value in cardiac edema, acute glaucoma, epilepsy, obesity, toxemias and edema of pregnancy, the action of DIAMOX is considered a welcome departure from that of the mercurials.[1] It is well tolerated orally and even when given in large dosage side effects are rare.[2] Excretion by the kidney is complete within 24 hours with no cumulative effects.[2]

A safe, versatile drug, DIAMOX is effective not only in the mobilization of edema fluid but in the prevention of fluid accumulation as well.[2] A single dose is active for 6 to 12 hours, offering convenient daytime diuresis.

Supplied: Scored Tablets of 250 mg. (Also in ampuls of 500 mg. for parenteral use in critical cases).

1 Krantz, J. C. and Carr, C. J.: The Pharmacologic Principles of Medical Practice. Ed. 3. The Williams & Wilkins Co., Baltimore, 1954, p. 1014.

2 Goodman, L. S. and Gilman, A.: The Pharmacological Basis of Therapeutics. Ed. 2. The Macmillan Co., New York, 1955, p. 856.

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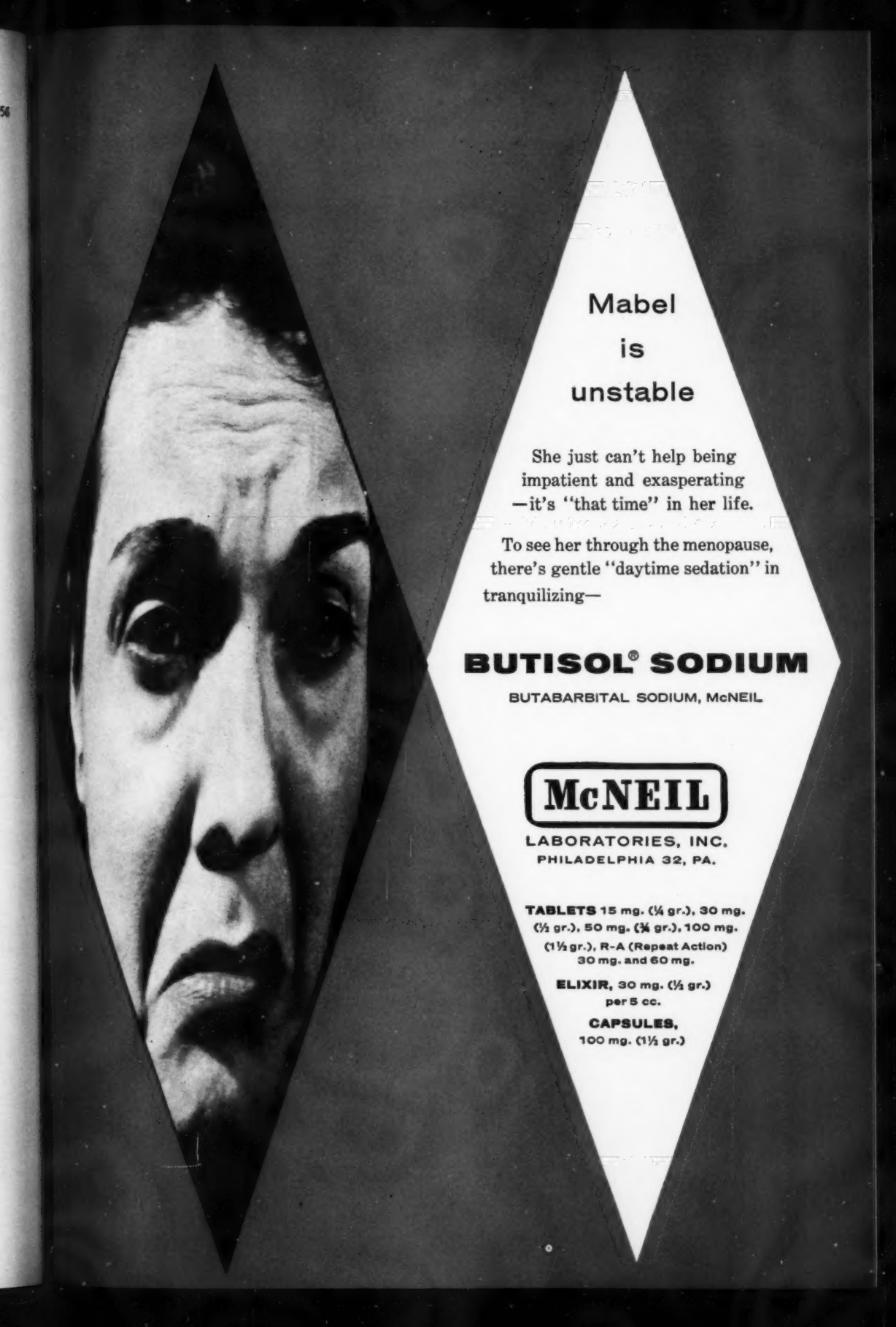
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TABLETS 15 mg. (¼ gr.), 30 mg. (½ gr.), 50 mg. (¾ gr.), 100 mg. (1½ gr.), R-A (Repeat Action) 30 mg. and 60 mg.
ELIXIR, 30 mg. (½ gr.) per 5 cc.
CAPSULES, 100 mg. (1½ gr.)

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(ethylnorepinephrine Breon)

As asthma advances in chronicity from mild through moderate to severe, few things are more disheartening to the physician (and frightening to the patient) than a parallel advance in drug tolerance. Increases in dosage often produce no more than an increase in side effects. It's a therapeutic point of no return that developing complications, emphysema and bronchostenosis, serve to emphasize.

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Going a step further, BRONKEPHRINE's low level of excitation,[1,2,3] described as much less than that of epinephrine,[3] is not only a strong reason for its use in asthma in children,[1] but is also a factor favoring its use in *any* asthmatic.

However important BRONKEPHRINE's lack of tolerance and lack of excitation may be, its lack of pressor action, compared with other agents, is "most notable."[1] BRONKEPHRINE's potent bronchodilating action is distinguished by its *lack* of pressor effects.[1,3-6] This means that even hypertensive asthmatics may now receive effective anti-asthmatic therapy without the risk of increased blood pressure.

BRONKEPHRINE® (ethylnorepinephrine Breon), for either intramuscular or intravenous injection—*your* drug of choice for *any* asthmatic—is available in 10 cc. multidose vials, containing 2 mg. BRONKEPHRINE in each cc.

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With only one to four injections of Protamide® prompt and complete recovery was obtained in 84% of all herpes zoster patients and in 96% of all neuritis patients treated during a five-year period by Drs. Henry W., Henry G., and David R. Lehrer (Northwest Med. 75:1249, 1955).

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METICORTEN (PREDNISONE) PLUS CHLOR-TRIMETON WITH ASCORBIC ACID

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quickly clears nasal passages • avoids rebound engorgement and sympathomimetic side effects • safe even for cardiacs, hypertensives, children, pregnant patients •

Composition: Contains 2 mg. (0.2%) METICORTELONE acetate (prednisolone acetate) and 3 mg. (0.3%) of CHLOR-TRIMETON gluconate (chlorprophenpyridamine gluconate) in each cc.

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The Original Alseroxylon Fraction of India-Grown Rauwolfia Serpentina, Benth.

The isolation of rescinnamine,[1] another potent alkaloid in Rauwolfia serpentina, has substantiated two important points:

A—It discredits the erroneous opinion that reserpine is *the* sole active principle of Rauwolfia;[2]

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Pharmacologic and clinical evaluation has shown rescinnamine to be similar to reserpine in antihypertensive activity, but to be considerably less sedative and much less apt to lead to lethargy and mental depression.[4, 5]

The interaction of reserpine, rescinnamine, and other contained alkaloids may well account for the balanced and desirable clinical behavior of Rauwiloid.

1. Kloha, M.W.; Draper, M.D., and Keller, F.: Alkaloids of Rauwolfia Serpentina Benth. III. Rescinnamine, a New Hypotensive and Sedative Principle, J. Am. Chem. Soc. 76:2843 (1954).
2. Cronheim, G.; Brown, W.; Cawthorne, J.; Tookes, M.I., and Ungari, J.: Pharmacological Studies with Rescinnamine, a New Alkaloid Isolated from Rauwolfia Serpentina, Proc. Soc. Exper. Biol. & Med. 86:120 (May) 1954.
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4. Hershberger, R.; Hughes, W., and Dennis, E.: Clinical Results in the Treatment of Hypertension with Rescinnamine, Clin. Res. Proc. 3:71 (Feb.) 1955.
5. Smirk, F.H., and McQueen, E.G.: Comparison of Rescinnamine and Reserpine as Hypotensive Agents, Lancet 2:115 (July 16) 1955.

The dosage of Rauwiloid is simple and definite: Merely two 2 mg. tablets at bedtime. For maintenance, one tablet usually suffices.

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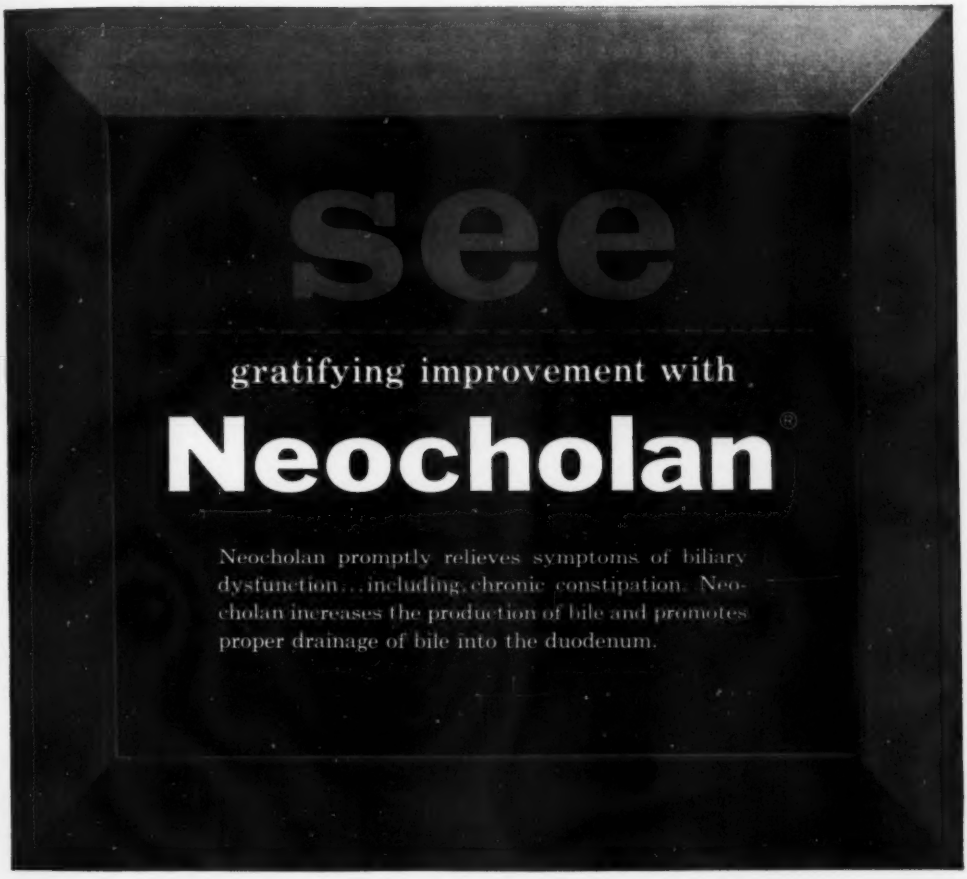
LOOK for other signs of biliary dysfunction in "chronic constipation" patients

Other symptoms of dyspepsia, such as flatulence, intestinal atony, and belching—along with the patient's chronic constipation—may indicate a functional disorder of the biliary tree.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Neocholan promptly relieves symptoms of biliary dysfunction...including chronic constipation. Neocholan increases the production of bile and promotes proper drainage of bile into the duodenum.

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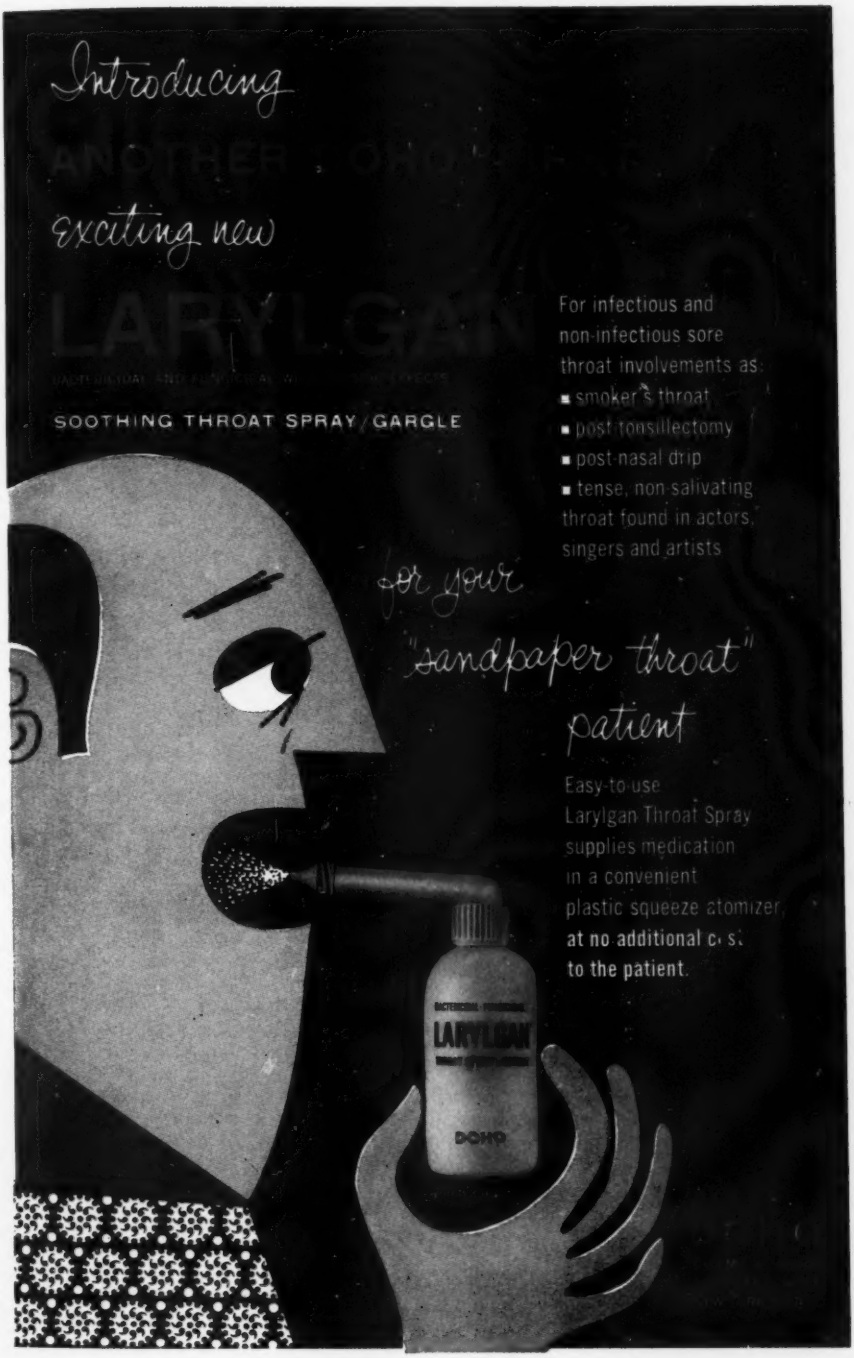
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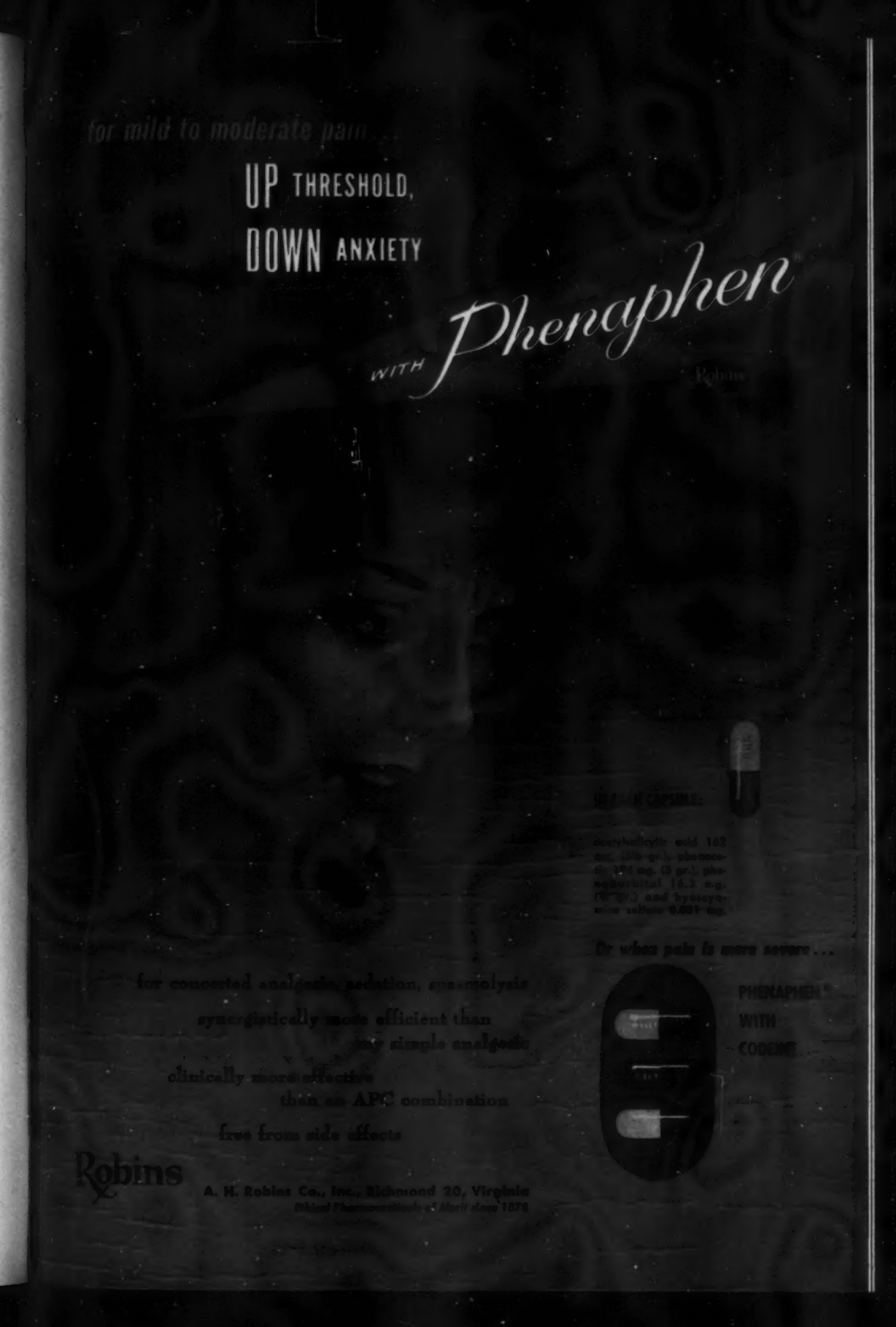

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even in many cases of
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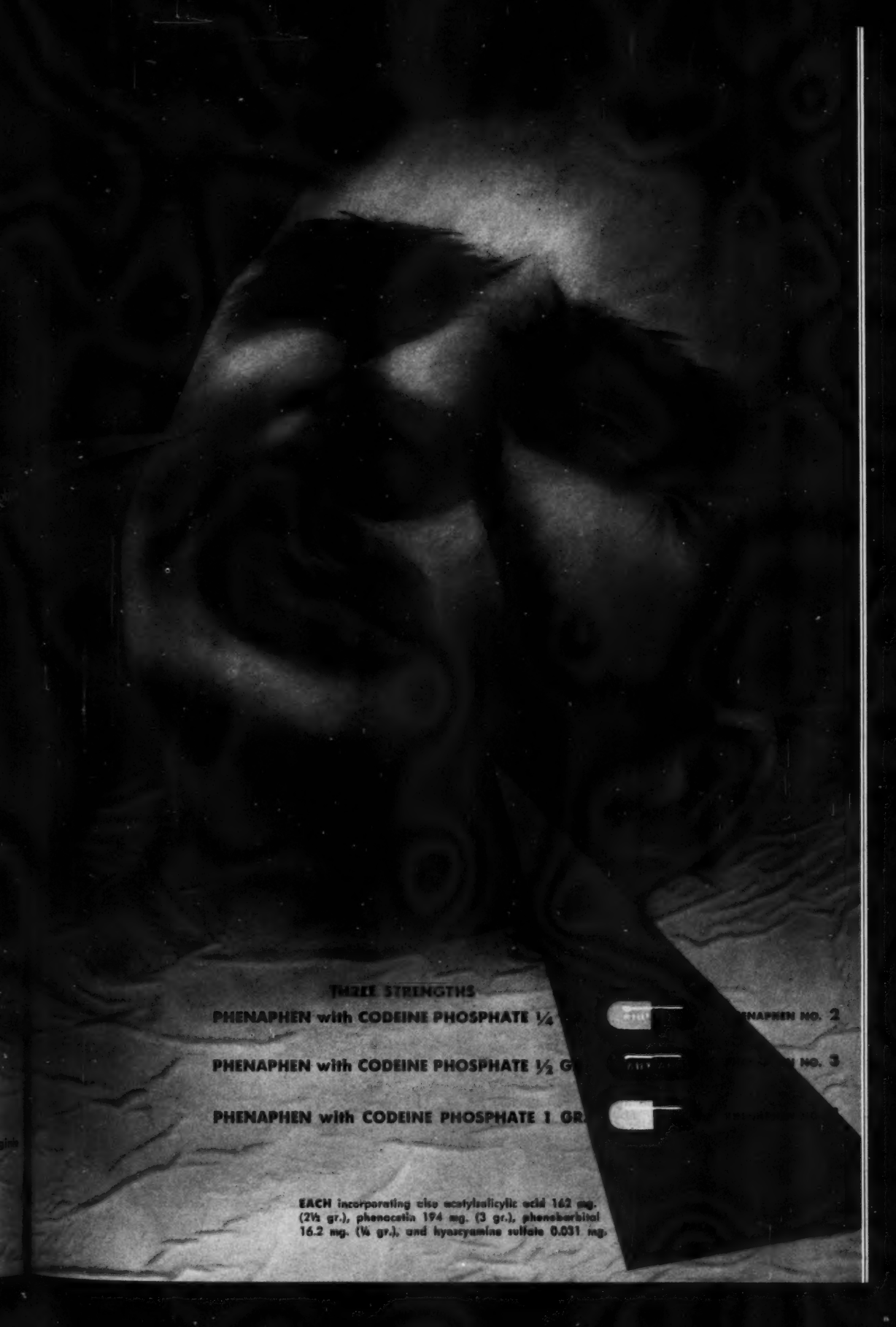
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reduces hyperperistalsis
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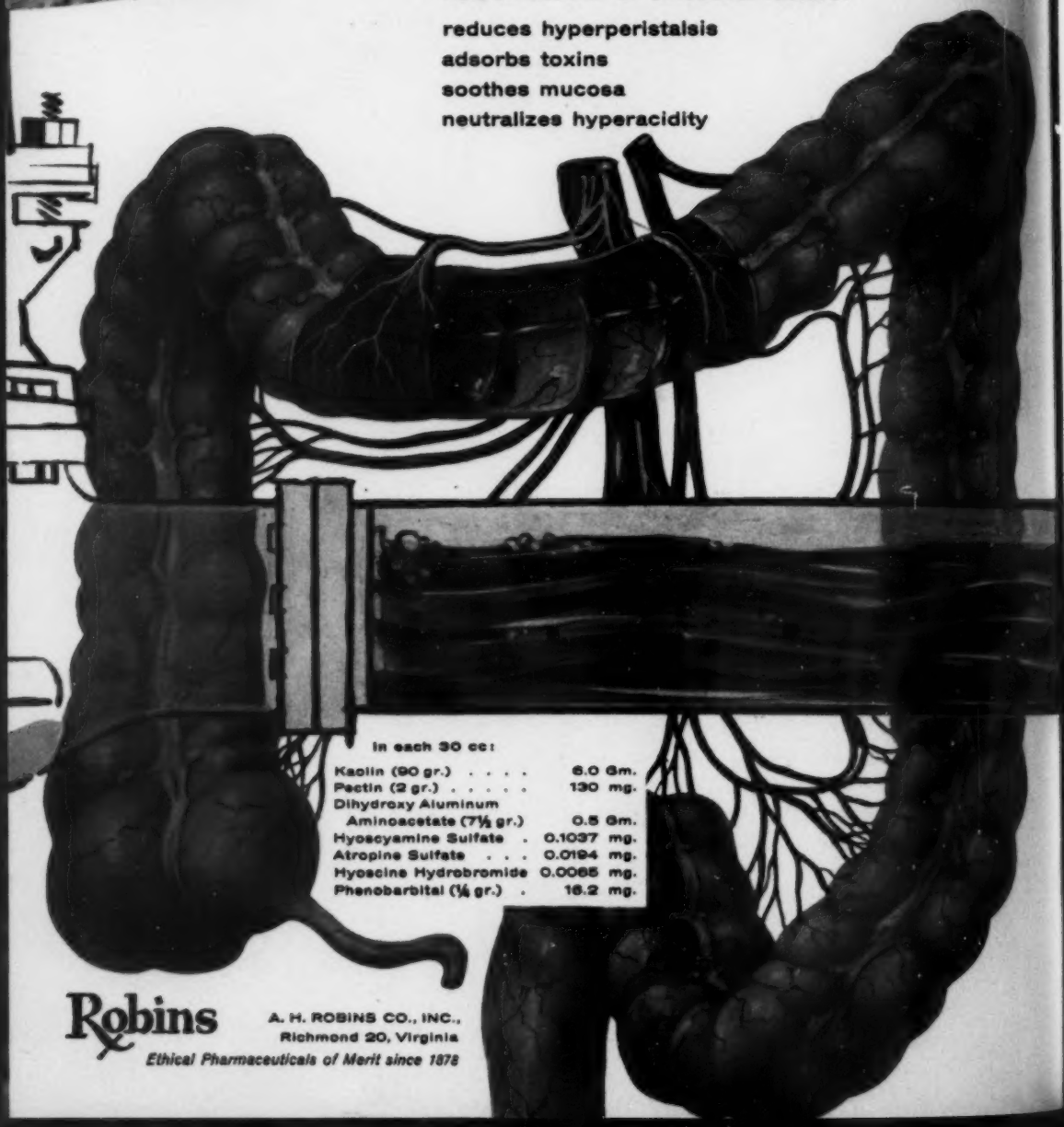

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Thiamine Mononitrate (B_1)	5 mg.	Vitamin E (as tocopheryl acetates)	10 I.U.	Copper (as CuO)	1 mg.
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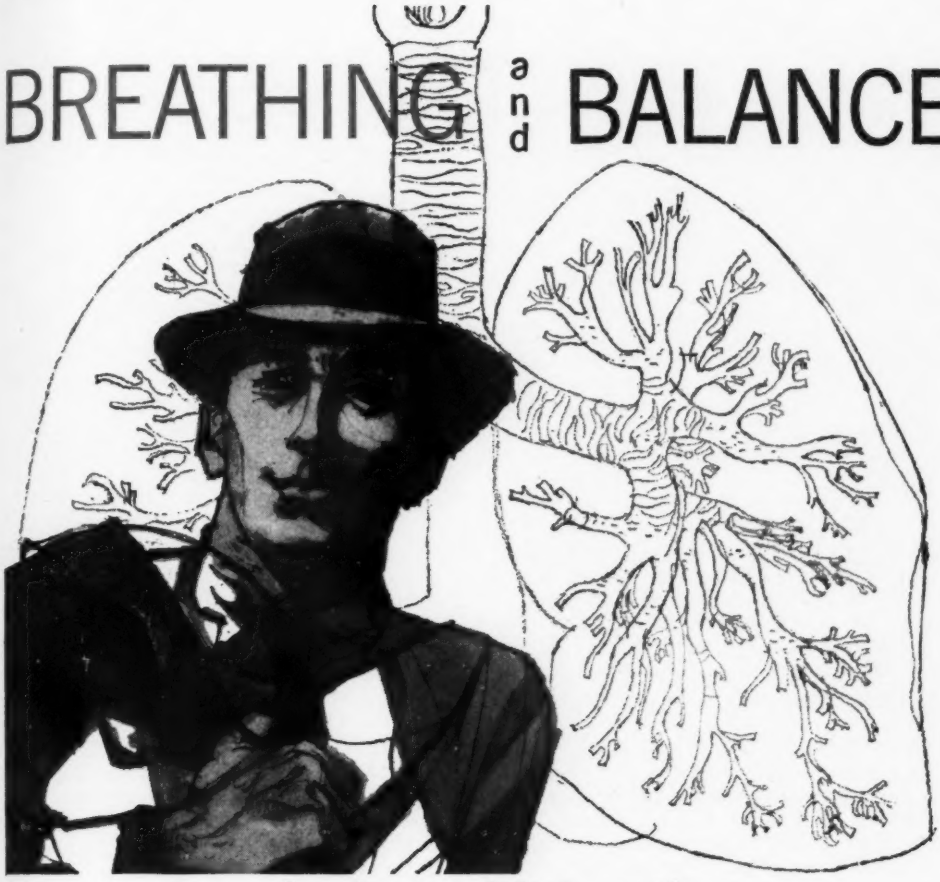
BREATHING and BALANCE



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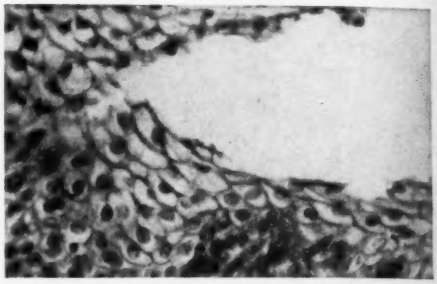

TOO OFTEN AN ORDINARY trichomonacide fails to cure vaginal trichomoniasis because it has little or no effect on parasites that are not on the surface.[1] Trichomonads burrowed deeply into the roughened mucosa survive and set up new foci of infection. In fact, even a few hidden trichomonads remaining after treatment can cause acute exacerbations. With VAGISEC® liquid and jelly you can overcome this most troublesome problem.

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References: 1. Davis, C. H., and Grand, C. G.: Am. J. Obst. & Gynec. 68:559 (Aug.) 1954. 2. Davis, C. H.: J.A.M.A. 157:126 (Jan. 8) 1955. 3. Davis, C. H.: West. J. Surg. 63:53 (Feb.) 1955. 4. Davis, C. H. (Ed.): Gynecology and Obstetrics (revision), Hagerstown, W. F. Prior, 1955, vol. 3, chap. 7, pp. 23-33. 5. Lanceley, F., and McEntegart, M. C.: Lancet 1:668 (Apr. 4) 1953.

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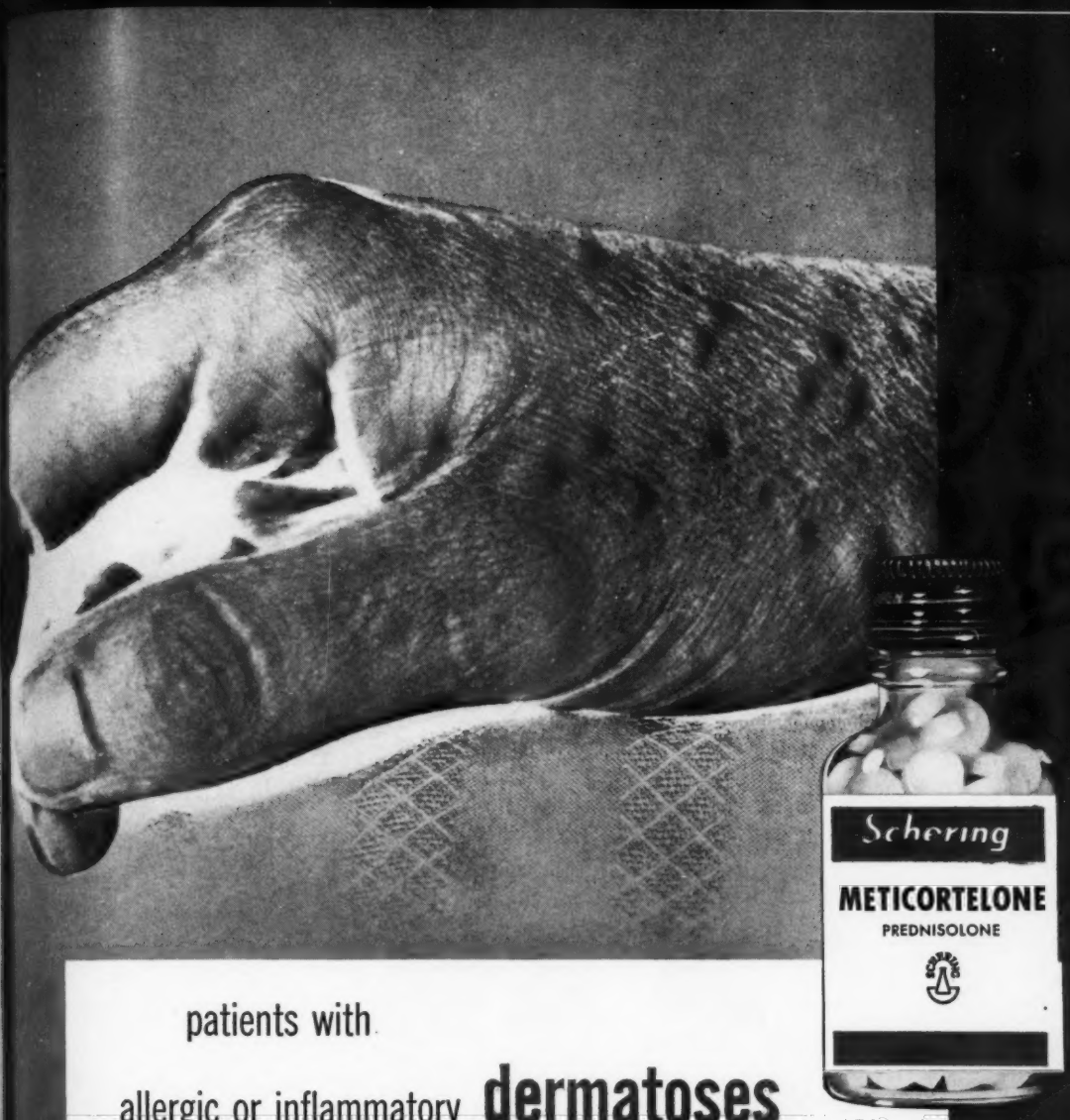

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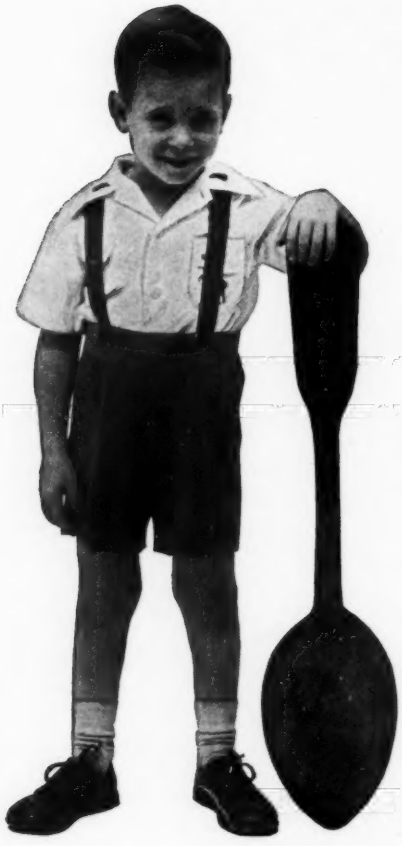

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1. Smith, R. T.; Kron, K. M.; Peak, W. P., and Hermann, I. F.: J.A.M.A. 160:745 (Mar. 3) 1956.

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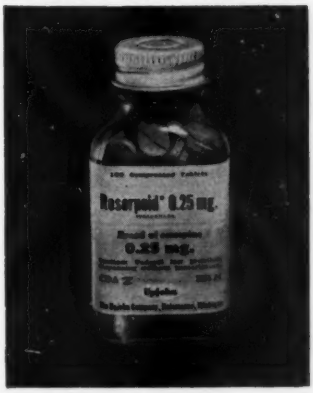

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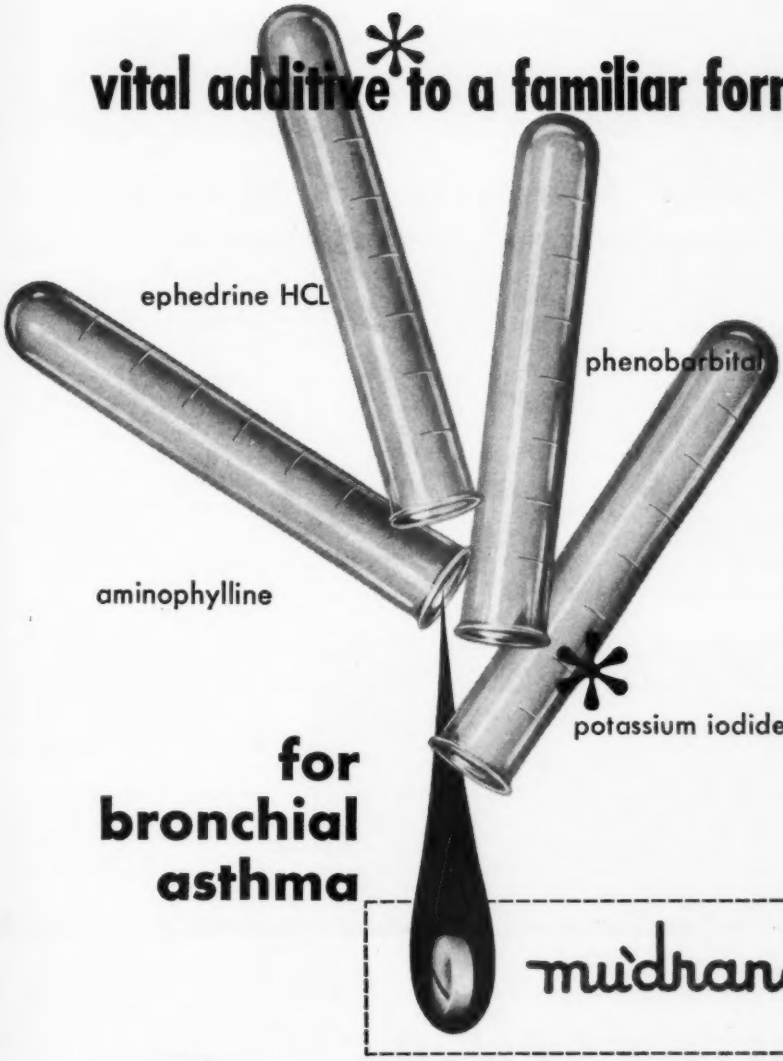

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1. Cohen, B.M.; Cross, E.B., and Johnson, W.: Am. Pract. 6: 1030, 1955.

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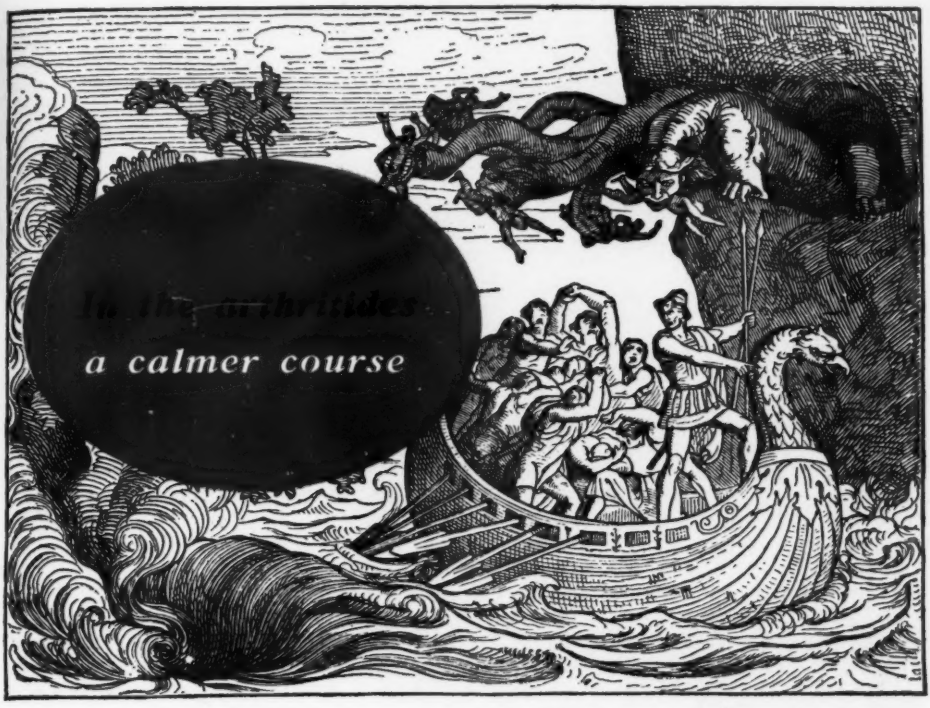

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[1] *Busse, E.A.: Treatment of Rheumatoid Arthritis by a Combination of Cortisone and Salicylates. Clinical Med.* 11:*1105*

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*Reifenstein, E. C., Jr.: The rationale for the use of anabolic steroids in controlling the adverse effects of corticoid hormones upon protein and osseous tissues. Southern M. J. 49: September, 1956.

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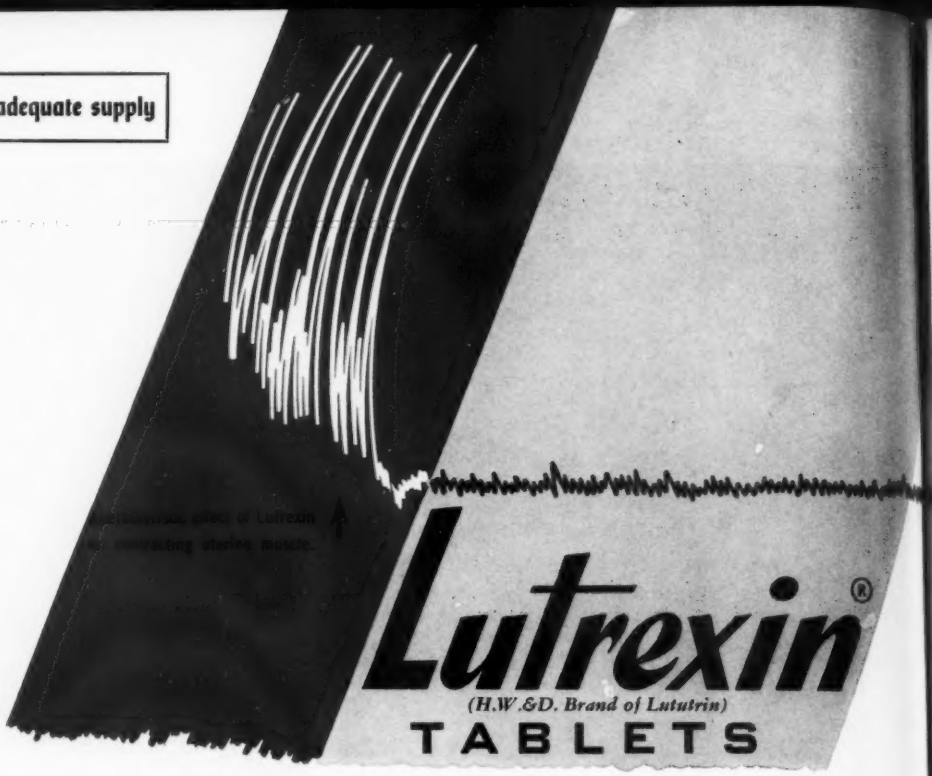

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1. *Rezek, G. H.: Am. J. Obstet. Gynecol., Vol. 66: No. 2, 396-402, 1953.*
2. *Jones, Georgeanna S. and Smith, Frank: Am. J. Obstet. Gynecol., Vol. 67: No. 3, 628-633, 1954.*
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Southern Medical Journal

PUBLISHED BY SOUTHERN MEDICAL ASSOCIATION

September 1956

The Rationale for the Use of Anabolic Steroids in Controlling the Adverse Effects of Corticoid Hormones Upon Protein and Osseous Tissues*

EDWARD C. REIFENSTEIN, JR., M.D.,† *New York, N. Y.*

I. Introduction

II. Evidence from the Literature

POINT 1: *The Effects of Corticoid Hormones upon Protein and Osseous Tissues*

A. Observations

1) *Effects of Endogenous Corticoid Hormones*

2) *Effects of Administered Corticoid Hormones*

3) *Conclusion from Observations*

B. Interpretation of Mechanism

POINT 2: *The Effects of Androgenic and/or Estrogenic Hormones upon Protein and Osseous Tissues*

A. Observations

1) *Effects of Endogenous Gonadal Hormones*

2) *Effects of Administered Gonadal Hormones*

3) *Conclusion from Observations*

B. Interpretation of Mechanism

POINT 3: *The Effects of Anabolic Steroids in Combination with Corticoid Hormones upon Protein and Osseous Tissues*

A. Observations

1) *Combined with Endogenous Corticoids*

2) *Combined with Administered Corticoids*

3) *Conclusion from Observations*

B. Interpretation of Mechanism

III. Clinical Implications

IMPLICATION 1: *For Pathologic Physiology and Mechanisms of Disease*

A. Endogenous Excess of Corticoids

1) *Absolute Excess*

a) *Cushing's Syndrome*

2) *Relative Excess*

a) *The Normal Child*

b) *Old Age*

c) *The Postmenopausal Woman*

d) *Hypogonadism Associated with Normal Adrenal Cortical Function*

B. Exogenous Excess of Corticoids

1) *Corticoid Therapy*

2) *Susceptibility to Adverse Effects upon Protein and Osseous Tissues*

IMPLICATION 2: *For Therapy with Anabolic Steroids*

A. Indications for Therapeutic Use

B. Indications for Preventive Use

C. Regulation of Dosage

D. Practical Therapy

IV. Discussion

1. *The Action of Corticoid Hormones*
2. *Anabolic Versus Gonadal Actions of Steroids*
3. *The Recognition of Tissue Depletion*
4. *The Recognition of Tissue Repletion*

V. Conclusions

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*Read before the Section on Medicine, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

†Associate Medical Director, Medical Division, The Squibb Institute for Medical Research, E. R. Squibb & Sons Division, Olin Mathieson Chemical Corporation, New York, N. Y.; Assistant Clinical Professor of Medicine, New York Medical College, New York, N. Y.

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VI. Summary
VII. References

Introduction

CORTICOID MATERIALS [adrenocorticotropic hormone (ACTH), hydrocortisone (cortisol), cortisone, and related steroids] are employed extensively at the present time as therapeutic agents. Two methods are available to physicians for maintaining abnormally increased levels of cortical hormones in man: (1) the administration of ACTH, and (2) the administration of hydrocortisone, cortisone and related steroids. In this presentation, it will be assumed that the effects produced by these two methods of hormone administration are identical, and the term corticoid materials (hormones, substances, or agents) will be employed as a general designation for both types of hormone preparation.

The dramatic beneficial response of patients with a variety of conditions to corticoid hormones is well known, and will not be discussed here. As a consequence of these therapeutically useful effects, however, many patients now are being maintained on continuous therapy with ACTH or cortical steroids for months or even years. From the outset, physicians have been mindful of certain potential dangers that accompany the chronic administration of these potent corticoid hormone preparations, and have decreased these hazards by such measures as: (1) reducing the dosage of the corticoid materials to the minimum amount that will control the underlying disease; (2) administering the medications intermittently when this was possible; and (3) supplying substances such as potassium that tend to be depleted by the therapy.[1-10] In spite of such procedures, however, these corticoid substances may have adverse effects on protein and osseous tissues.

The objectives of this presentation are: (1) to emphasize the nature and the frequent occurrence of the unfavorable effects of corticoid hormones upon the protein and osseous tissues; (2) to review the favorable actions of anabolic gonadal steroids upon these tissues; (3) to cite evidence that anabolic steroids are effective in countering and controlling these undesirable manifestations; (4) to discuss some of the clinical implications of these observations for the pathologic physiology and mechanisms of certain disorders and for the application of anabolic steroids in therapy; and (5) to urge the administration of anabolic steroids in order to protect and/or restore protein and osseous tissues in patients who are being given prolonged and/or intensive corticoid therapy, or even moderate "physiologic" amounts of corticoids when endogenous anabolic hormone levels are low (as in panhypopituitarism, or in Addison's disease with hypogonadism), and in patients who have either an absolute excess of endogenous cortical steroids (as in Cushing's syndrome associated with benign lesions) or a relative excess of endogenous cortical steroids (as in old age, the postmenopausal state, or hypogonadism associated with normal adrenal cortical function).

Evidence From the Literature

POINT 1: *The Effects of Corticoid Hormones Upon Protein and Osseous Tissues*

A. Observations

Evidence for the effect of corticoid hormones on protein and osseous tissues can be derived from two sources: (1) the manifestations that occur spontaneously in patients who have an endogenous excess of such hormones in Cushing's syndrome, and (2) the manifestations that appear in patients who have received such hormones as therapy for prolonged periods.

1) *Effects of Endogenous Corticoid Hormones*

Cushing's syndrome is now generally accepted to result from an hyperadrenocorticism with an excessive production and/or release of the cortical hormone, hydrocortisone (cortisol), and its derivative, cortisone.[9,11,12] The manifestations of the syndrome arise from the excess of these hormones. Certain of the characteristic clinical features of patients with Cushing's syndrome obviously involve the protein and osseous tissues. These features include:[9,11] (1) a thin skin, which is reddish in hue (as a consequence of its transparency), and which frequently is marked with purplish striae at the points of stretching (as a consequence of its friability and cracking); (2) ease of bruising (as a consequence of an atrophy of the walls of the blood vessels); (3) weakness, marked muscular wasting, and relaxation of the abdominal wall (as a consequence of an atrophy of the muscles); and (4) osteoporosis, a metabolic bone disorder with an atrophy of bones [as a consequence of inadequate formation of protein matrix (osteoid)

and hence of reduced formation of calcified bone]. Furthermore, a negative nitrogen balance has been observed in some patients with Cushing's syndrome during metabolic balance studies.[2,9,11,12]

Osteoporosis is one of the most common serious manifestations of Cushing's syndrome. It was present in 39 patients among the 43 unpublished cases studied by the Fuller Albright group at the Massachusetts General Hospital,[13] and in 53 of the 61 cases reported by Eisenhardt and Thompson.[14] The osteoporosis appeared as soon as several months after recognition of the pathologic state of Cushing's syndrome by the patient and frequently produced back pain, occasionally with radicular distribution. The serum calcium, inorganic phosphorus, and alkaline phosphatase levels were normal, but the urinary calcium excretion was increased in most of the patients tested. Roentgenograms demonstrated a generalized increased radiolucency of the bones which was most marked in the spine and ribs. Also characteristic were increased or decreased trabecular markings, dense end-plates as compared with the central portion of the vertebrae, widening of the intervertebral spaces, and finally collapse of the vertebrae, most commonly in the lumbar and thoracic areas.

The four manifestations of Cushing's syndrome which have been mentioned are unequivocal evidence of depletion of the protein component of the skin, the blood vessels, the muscles, and the bones;[2] they indicate that endogenous corticoid hormones have a profound adverse effect upon protein and osseous tissues.

2) *Effects of Administered Corticoid Hormones*

Since the manifestations of Cushing's syndrome arise from an endogenous excess of corticoid hormones, it was anticipated that all of these same findings would be induced by an excess of corticoid hormones created by the administration of ACTH or cortical steroid agents if the therapy was given continuously in large amounts and/or for a sufficiently long period of time. It is now a matter of record that almost all of the manifestations of Cushing's syndrome have been observed during the course of such chronic therapy in patients who prior to treatment had no evidence of adrenal dysfunction.[1-4,6,10,13,15-25] The state of these patients has been described as corticoid "poisoning," or "Cushing's syndrome medicamentosa." The identical manifestations involving the protein and osseous tissues have been reported: (1) a thin skin of reddish hue showing the characteristic distribution of purplish striae; (2) ease of bruising; (3) weakness, marked muscular wasting, and relaxation of the abdominal wall; and (4) osteoporosis. The disturbance in bone metabolism of patients on chronic corticoid medication is indicated by spontaneous pathologic fractures in some patients in whom the therapy with corticoid hormones has been continued for considerable periods of time and/or at large doses.[13,15-18,22-34]

A partial survey (Tables 1 and 2, and Fig. 1) revealed 38 cases with spontaneous fractures following corticoid therapy. The following points are apparent:

(1) The occurrence of spontaneous fractures is related to both the amount and the duration of therapy with corticoid materials.

(2) Spontaneous fractures may result from treatment with cortisone, hydrocortisone, or ACTH. Before fracture, the approximate dosage of cortisone ranged from 3.4 to 83 Gm., of hydrocortisone from 9.7 to 13.4 Gm., and of ACTH from 0.14 to 42 Gm. The duration of therapy before fracture ranged from approximately one month to over three years (34 to 1,148 days). If it is assumed that the same dosage of corticoid materials was administered each day from the initiation of therapy to the occurrence of fracture, the amount of therapy in 26 cases (Table 2) ranged from 41 to 150 mg. per day.

When no other factors are considered except the dosage and the duration of therapy, the approximate time that a given dose can be administered daily *in an adult* before a spontaneous fracture may occur can be estimated from the following equation: the occurrence of fracture = 900 (± 200) days *minus 5 times* the dosage in milligrams per day. This formula does not take into consideration many factors (such as the status of the bones at the time that the therapy is started; the physical activity, the sex, the endogenous hormone balance, the acid-base equilibrium, and the renal and gastrointestinal tract function of the patient; the mineral and protein intake during the corticoid therapy; and so forth) which obviously will influence the time of occurrence of the adverse effects of corticoid therapy in a given individual. The equation, therefore, will give only a rough estimate of the potential danger period. For example, on a dosage of 100 mg. of corticoid medication per day, the average danger point would be reached after about 400 days of therapy, although fracture may occur as soon as 200 days after the start of treatment, or it may not appear until after 600 days of medication.

(3) Spontaneous fractures with corticoid therapy occurred in nearly twice as many females as males.

(4) Spontaneous fractures with corticoid therapy occurred much more frequently in the vertebra than in other bones.

(5) Approximately three times as many cases of spontaneous fractures following corticoid therapy were reported from 1953 through 1955 as were reported from 1950 through 1952. This may be an indication of the increase in the use of chronic corticoid therapy, and of the fact that spontaneous fractures are late complications of such therapy.

(6) From the point of view of the duration of corticoid therapy before spontaneous fracture, the

TABLE 1

REPORTED CASES OF SPONTANEOUS FRACTURE IN PATIENTS ON CHRONIC CORTICOID THERAPY

Author	Date Reported	Case No.	Patient Identification	Sex	Age	Diagnosis	Amount of Corticoid Therapy Before Fracture*				Duration of Therapy Before Fracture* (days)	Status of Bones Before Therapy	Bones Fractured
							Cortisone (grams)	Hydrocortisone (grams)	ACTH (grams)	Total Therapy (grams)			
Boland and Headley (15)	Sept. 1950	1	n.s.	F	70	Rheumatoid arthritis	3.4	—	—	3.4	34	Osteoporosis	Femur
		2	n.s.	M	65	Rheumatoid arthritis	7.3	—	—	7.3	73	Osteoporosis	Vertebra
Steinbrocker, et al. (16)	Sept. 1951	1	n.s.	F	n.s.	Rheumatoid arthritis	n.s.	n.s.	n.s.	n.s.	n.s.	Mild osteoporosis	Vertebra
		2	n.s.	F	n.s.	Periarthritis of shoulder	n.s.	n.s.	n.s.	n.s.	n.s.	Mild osteoporosis	Humerus
Demartini, et al. (26)	June 1952	1	C.M.	F	47	Rheumatoid arthritis	70.0	—	—	70.0	600	Osteoporosis	Vertebrae
		2	E.K.	F	61	Strümpell-Marie arthritis	23.5	—	—	23.5	330	Osteoporosis	Vertebra
		3	M.S.	F	45	Rheumatoid arthritis	38.7	—	—	38.7	330	Osteoporosis	Vertebrae
		4	C.H.	F	53	Rheumatoid arthritis	6.3	—	—	6.3	60	Osteoporosis	Vertebrae
		5	L.D.	F	58	Strümpell-Marie arthritis	6.8	—	—	6.8	90	Osteoporosis	Vertebrae
Soffer, et al. (17, 18)	July 1952	1	n.s.	F	58	Lupus erythematosus	n.s.	n.s.	n.s.	n.s.	n.s.	Some osteoporosis	Vertebra
Teicher and Nelson (27)	Sept. 1952	1	E.M.	M	48	Pemphigus vulgaris	82.975	—	5.235	88.2	961	Normal by x-ray	Vertebrae
Case Records M.G.H. (28)	May 1953	1	n.s.	F	43	Pemphigus vulgaris	n.s.	n.s.	n.s.	n.s.	n.s.	Normal by x-ray	Vertebrae
de Sèze, et al. (29)	June 1953	1	n.s.	n.s.	n.s.	n.s.	7.0	—	—	7.0	70	n.s.	Vertebra
		2	n.s.	n.s.	n.s.	n.s.	25.0	—	1.8	26.8	200	n.s.	Vertebra
		3	n.s.	n.s.	n.s.	n.s.	18.0	—	—	18.0	215	n.s.	Femur
		4	n.s.	n.s.	n.s.	n.s.	3.5	—	—	3.5	n.s.	n.s.	Tibia
Welch and Forsyth (30); Luder (31)	June 1953	1	R.M.	M	11	Still's disease	11.825	—	—	11.825	236	Normal by x-ray	Vertebrae
Welch and Forsyth (30)	June 1953	2	W.C.	F	3	Still's disease	4.76	—	0.14	4.9	119	n.s.	Tibia
West and Newns (22)	Nov. 1953	1	n.s.	M	58	Rheumatoid arthritis	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	Femur
Irwin, et al. (13); Burrage, et al. (25)	May 1954	1	W.G.	M	60	Asthma	24.0	—	—	24.0	240	Severe osteoporosis	Vertebrae
Engleman, et al. (23)	May 1954	1	n.s.	F	77	Rheumatoid arthritis	n.s.	n.s.	n.s.	n.s.	n.s.	Severe osteoporosis	Vertebrae
		2	n.s.	F	52	Rheumatoid arthritis	n.s.	n.s.	n.s.	n.s.	n.s.	Severe osteoporosis	Vertebrae
Luder (31)	June 1954	1	R.W.	M	3	Still's disease	24.75	—	—	24.75	330	Normal by x-ray	Vertebrae
		2	R.D.	M	11	Rheumatoid arthritis	5.32	—	1.77	7.09	71	Normal by x-ray	Vertebrae
		3	H.S.	F	6	Leukemia	5.72	—	—	5.72	76	n.s.	Vertebrae
Curtiss, et al. (32)	Oct. 1954	1	n.s.	M	57	Rheumatoid arthritis	10.0	—	28.0	38.0	883	n.s.	Vertebrae
		2	n.s.	M	67	Rheumatoid arthritis	31.0	—	—	31.0	365	n.s.	Vertebra
		3	n.s.	M	9	Still's disease	45.0	—	2.5	47.5	478	n.s.	Vertebrae
		4	n.s.	M	63	Rheumatoid arthritis	27.0	—	—	27.0	206	n.s.	Vertebrae
Bunim, et al. (24)	Jan. 1955	1	n.s.	F	postmenopausal	Rheumatoid arthritis	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
		2	n.s.	F	postmenopausal	Rheumatoid arthritis	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
		3	n.s.	F	postmenopausal	Rheumatoid arthritis	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
		4	n.s.	F	postmenopausal	Rheumatoid arthritis	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Eisenstadt and Cohen (33)	May 1955	1	J.M.	M	57	Asthma	9.0	—	42.0	51.0	960	Normal by x-ray	Vertebrae
Burrage, et al. (25)	Nov. 1955	1	F.G.	F	47	Asthma	60.8	12.1	—	72.9	791	n.s.	Vertebrae
		2	A.F.	F	73	Asthma	43.2	—	—	43.2	865	n.s.	Vertebrae
		3	P.B.	M	72	Asthma	61.6	13.4	—	75.0	1148	n.s.	Vertebrae
		4	B.B.	F	52	Asthma	—	9.75	—	9.75	65	n.s.	Vertebrae

n.s. = not stated
*estimated from data when not stated specifically

TABLE 2

THE AMOUNT AND THE DURATION OF CORTICOID THERAPY BEFORE THE ONSET OF SPONTANEOUS FRACTURES IN 26 PATIENTS WITH VARIOUS DISORDERS

			Amount of Corticoid Therapy Before Fracture							
Age	Sex	Diagnosis	Cortisone (grams)	Hydrocortisone (grams)	ACTH (grams)	Total Therapy (grams)	Calculated Daily Dosage (mg./day)	Duration of Therapy Before Fracture (days)	Status of Bones Before Therapy	References
3	F	Still's disease	4.76	—	0.14	4.9	41	119	I	30
6	F	Leukemia	5.72	—	—	5.72	75	76	I	31
11	M	Rheumatoid arthritis	5.32	—	1.77	7.09	100	71	I	31
11	M	Rheumatoid arthritis	11.83	—	—	11.83	50	236	I	30, 31
3	M	Still's disease	24.75	—	—	24.75	75	330	I	31
9	M	Still's disease	45.0	—	2.5	47.5	100	478	I	32
70	F	Rheumatoid arthritis	3.4	—	—	3.4	100	34	O	15
53	F	Rheumatoid arthritis	6.3	—	—	6.3	105	60	O	26
58	F	Strümpell-Marie arthritis	6.8	—	—	6.8	75	90	O	26
n.s.	n.s.	n.s.	7.0	—	—	7.0	100	70	n.s.	29
65	M	Rheumatoid arthritis	7.3	—	—	7.3	100	73	O	15
52	F	Rheumatoid arthritis	—	9.75	—	9.75	150	65	n.s.	25
n.s.	n.s.	n.s.	18.0	—	—	18.0	84	215	n.s.	29
61	F	Strümpell-Marie arthritis	23.5	—	—	23.5	71	330	O	26
60	M	Asthma	24.0	—	—	24.0	100	240	O	13, 25
n.s.	n.s.	n.s.	25.0	—	1.8	26.8	134	200	n.s.	29
63	M	Rheumatoid arthritis	27.0	—	—	27.0	131	206	n.s.	32
67	M	Rheumatoid arthritis	31.0	—	—	31.0	85	365	n.s.	32
57	M	Rheumatoid arthritis	10.0	—	28.0	38.0	43	883	n.s.	32
45	F	Rheumatoid arthritis	38.7	—	—	38.7	117	330	O	26
73	F	Asthma	43.2	—	—	43.2	50	865	n.s.	25
57	M	Asthma	9.0	—	42.0	51.0	53	960	n.s.	33
47	F	Rheumatoid arthritis	70.0	—	—	70.0	117	600	O	26
47	F	Asthma	60.8	12.1	—	72.9	92	791	n.s.	25
72	M	Asthma	61.6	13.4	—	75.0	65	1148	n.s.	25
48	M	Pemphigus vulgaris	82.975	—	5.235	88.2	92	961	N	27

I = immature
N = normal by x-ray
n.s. = not stated
O = osteoporotic

patients seem to fall in two groups: (a) children, and persons of middle age and beyond who develop the complication within the first one and one-half years of therapy; and (b) middle-aged and elderly persons who do not develop the complication until they have been treated for over two years. The reason for this difference is not clear; it may be related to the status of the bones before therapy. In the early group, the bones were immature or described as osteoporotic before therapy in 13 cases; in 6 cases of this group the status of bones prior to medication was not stated. In the 7 patients of the late group, the status of the bones before therapy was described as normal by x-ray in 1 case, osteoporotic in 1 case, and not stated in 5 cases.

(7) Spontaneous fractures following corticoid therapy are prone to occur particularly in: (a) patients with pre-existing osteoporosis, (b) persons of middle and advanced age, (c) postmenopausal women, (d) children, (e) individuals with marked restriction of activity or enforced bed rest, and (f) patients who are given corticoid materials in large amounts and/or for prolonged periods.

The disturbance in bone metabolism of patients on chronic corticoid medication is indicated also by persistent hypercalcuria.[13]

The urinary calcium excretion of 21 asthmatic patients on corticoid therapy is shown in figure 2. Attention is called to the fact that 14 of the 21 patients had at least one urinary calcium value of over 150 mg. per 24 hours; 9 patients had no values under 150 mg. per 24 hours. Of the total of 56 determinations, 31 were over 150 mg. per 24 hours.

It has been demonstrated by metabolic balance studies that under the influence of corticoid hormones there is an increased excretion of nitrogen and phosphorus consistent with a loss of protein tissues.[1-3, 9, 35-37]

The effect of cortisone and of adrenocorticotropic hormone (ACTH) upon the urinary nitrogen excretion and upon the nitrogen balance of patients with various disorders is illustrated in figures 3, 12, and 13. Attention is called to the fact that losses of over 60 mg. of nitrogen per Kg. per day were induced by these corticoid materials.

The manifestations of "Cushing's syndrome medicamentosa," like those of true Cushing's syndrome, again are unequivocal evidence of depletion of the protein component of the skin, the blood vessels, the muscles, and the bones. The findings in man are supported by numerous observations in a variety of animal species that corticoid hormones under suitable circumstances have adverse effects on protein metabolism, on the protein tissues of the skin, the blood vessels, the muscles, and the bones, and on growth.[40-52]

3) *Conclusion from Observations*

The evidence indicates, therefore, that corticoid hormones (whether endogneous in origin or administered) frequently have un-

favorable effects upon protein and osseous tissues characterized by protein depletion and osteoporosis.

B. Interpretation of Mechanism

In the healthy adult individual, the metabolic activities concerned with the maintenance of protein and osseous tissues are in a state of dynamic equilibrium (Fig. 4, A). The two processes of anabolism and catabolism are proceeding at rates which result in the formation of new tissue and the breakdown of old tissue in exactly the same amounts per unit of time so that the integrity of the organism as a whole is maintained. A decrease in the total mass of protein or osseous tissues could be brought about by one of three mechanisms: (1) the rate of catabolism could be increased without a change in the rate of anabolism (Fig. 4, B); (2) the rate of anabolism could be decreased without a change in the rate of catabolism (Fig. 4, C); or (3) under extreme circumstances, the total mass could be depleted by a combination of an increase in the rate of catabolism and a decrease in the rate of anabolism (Fig. 4, D). The exact manner in which hormones, steroids, and related agents induce such changes in the rates of these biologic processes remains to be elucidated.

The author favors the interpretation that under most circumstances corticoid hormones have an anti-anabolic rather than a catabolic effect on protein and osseous tissues.

Some of the evidence is summarized as follows:

(1) When patients with Cushing's syndrome are in a negative nitrogen balance, the excessive excretion of nitrogen in the urine can be reduced to the normal amount by supplying in the diet additional carbohydrate and fat.[12] *If corticoid hormones were catabolic, loss of nitrogen in the urine would be independent of the carbohydrate and fat intake.*

(2) Patients with Cushing's syndrome in nitrogen equilibrium excrete approximately twice as much radioactive nitrogen from ingested labeled amino acids as do normal subjects.[53, 54] *If corticoid hormones were catabolic, the amounts of ingested amino acids that are not utilized for protein synthesis and hence are available for degradation and excretion would be the same in Cushing's syndrome and in the normal state.*

(3) The administration of ACTH to normal subjects increases the excretion of radioactive nitrogen from ingested labeled amino acids by 30 to 50 per cent.[53, 54] *If corticoid hormones were catabolic, the amounts of ingested amino acids that are not utilized for protein synthesis and hence are available for degradation and excretion would not change.*

(4) The rate of growth is markedly retarded in children with Cushing's syndrome.[12,55,56] In animals, corticoid hormones inhibit spontaneous growth,[49,50] and likewise inhibit the action of administered growth hormone.[51] *If corticoid hormones were catabolic, growth would not be inhibited, since increased catabolism cannot prevent bone anabolism.*

(5) By microscopic examination, the bone disease found in Cushing's syndrome and in patients chronically treated with corticoid medications proves to be osteoporosis (decreased bone formation) rather than osteitis fibrosa generalisata (increased bone resorption).[12] *The latter would be expected if corticoid hormones were catabolic.*

POINT 2. *The Effects of Androgenic and/or Estrogenic Hormones Upon Protein and Osseous Tissues*

A. Observations

Evidence for the effect of the gonadal hormones, androgen and estrogen, on protein and osseous tissues can be derived from the same two sources that were considered in evaluating the effects of corticoid hormones on these tissues: (1) the manifestations that occur spontaneously in patients who have an endogenous excess of these hormones; and (2) the manifestations that can be induced in patients by the administration of these hormones.

1) *Effects of Endogenous Gonadal Hormones*

In males, tumors of the testicular Leydig cells produce excessive quantities of androgen. The clinical manifestations of this hormone excess are remarkable. Boys with such tumors have somatic as well as sexual precocity, with exceptional growth in height, weight, musculature, and development of bone in addition to genitalia of adult size, a deep voice, a beard, masculine body hair, and the general habitus of a mature man.[57-72] Adults with malignant Leydig cell tumors maintain their vigor, strength and muscular mass until they die; they fail to lose weight or become debilitated in spite of extensive metastases.[73] One patient with a urinary 17-ketosteroid excretion of over 1,000 mg. per 24 hours sought medical assistance only after he began to have difficulty in swinging a pickax during his daily work as a laborer; examination revealed that he could not bend over because a tremendous cancer-studded liver was pressing against the bones of his pelvis.[74-76] In females, granulosa cell tumors of the ovary produce excessive amounts of estrogen. Girls with this rare tumor display not only sexual precocity and uterine bleeding, but also rapid

acceleration of skeletal growth, and occasionally excessive somatic development.[71,77-102]

In males with hypogonadism secondary to deficiency of pituitary gonadotropic hormones, the administration of chorionic gonadotropin stimulates the Leydig cells to increased production and/or release of endogenous androgenic hormones. Such therapy induces not only a pronounced development of the genital organs and accessory sexual structures, but also marked somatic alterations with an increase in musculature, a gain in weight, and an accelerated growth and maturation of bone.[103-109]

These manifestations in males and females with hormone-producing tumors of the gonad and in males in whom testicular hormone activity is stimulated by the use of chorionic gonadotropin are evidence that to a marked degree endogenous androgenic hormones, and to a lesser extent endogenous estrogenic hormones, have a stimulating effect upon the growth of protein and osseous tissues.

2) *Effects of Administered Gonadal Hormones*

As soon as potent androgenic compounds, such as testosterone and its derivatives, became available as therapeutic agents and were administered to sexually underdeveloped men and boys, it became apparent that these substances induced not only masculinization of the accessory sexual structures, but also a marked somatic development with an increase in muscle mass, a gain in weight, and an accelerated growth and maturation of bone.[110,111] In eunuchoid males, it has been demonstrated by metabolic balance studies that under the influence of androgenic steroids there is a retention of nitrogen, phosphorus, potassium, and sulfur in the proportions that are present in protein tissues.[70,105,112-123] Such quantitative measurements indicate clearly that growth of the accessory genitalia under this therapy accounts for very little of the retained material.[70] In more extended studies on hypergonadal males, it has been shown that with androgenic steroids there is also a retention of calcium and additional phosphorus in the proportions that are present in bone.[124-127] Similarly, the administration of potent estrogenic agents, such as estradiol and its derivatives, to sexually underdeveloped women and girls has been found to induce not only feminization of the accessory sexual structures, but also somatic development and acceleration of skeletal growth.[128-132] In such patients, it has been demonstrated by metabolic balance studies that under the influence of estrogenic steroids there are somatotropic effects on protein and osseous tissues which are qualitatively identical with those observed after the administration of androgenic compounds.[117] However, studies on men and women with various types of osteoporosis indicate that there are quantitative differences between the effects of testosterone compounds and those of estradiol compounds on the anabolism of protein and osseous tissues.[125,126,133-135]

The effect of testosterone propionate alone and in combination with estradiol benzoate upon the nitrogen and phosphorus balances of a patient with senile osteoporosis is illustrated in figure 5; the effect of these agents upon the calcium and phosphorus balances in the same metabolic balance study is illustrated in figure 6. Attention is called to the fact that these hormonal preparations induced a marked retention of nitrogen and phosphorus in the proportions that exist in muscle protoplasm (Fig. 5), and also a marked retention of calcium and additional phosphorus in the proportions that exist in bone (Fig. 6).

On protein tissue, testosterone agents have a greater anabolic effect than estradiol compounds, and the combination of both steroids together has no significantly greater effect than that of the testosterone substances alone. *On osseous tissue,* in contrast, estradiol agents have a greater anabolic effect than testosterone compounds, and the combination of both steroids together has a still more marked effect than that of the estradiol substances alone.[125,126,133-135]

The net retention of calcium, phosphorus, and nitrogen that was obtained during nine metabolic balance studies on patients with postmenopausal and senile osteoporosis by the prolonged administration of androgenic therapy alone, of estrogenic therapy alone, and of androgenic and estrogenic therapy in combination are summarized in figure 7. The findings indicate that androgen and estrogen have qualitatively identical but quantitatively different somatotropic effects on protein and osseous tissues.

Subsequent studies by many investigators indicate that the anabolic effects of these gonadal hormones (whether androgenic or estrogenic) can be induced under suitable conditions in persons of either sex who have a "normal" or "iso" status of their endocrine glands; in individuals who have glandular dysfunction secondary to hypothalamic damage; in patients who have underfunction of the anterior pituitary gland, the adrenal glands, the gonads, or the thyroid gland; in patients who have hyperfunction of the an-

terior pituitary gland, the adrenal glands, the thyroid gland, or the parathyroid glands; and in persons with all manner of chronic debilitating or acute wasting disorders accompanied by a negative nitrogen balance.[123,138] Furthermore, the anabolic effect of testosterone compounds has been demonstrated to occur even in patients on an inadequate protein and caloric intake who are utilizing tissue proteins for energy.[139-141]

The effect of testosterone propionate upon the nitrogen balance of an obese man on a low nitrogen and a low caloric intake is illustrated in figure 8. Note that during the administration of the testosterone ester under these drastic conditions, the urinary nitrogen excretion was reduced approximately 50 per cent so that the destruction of protein tissues was eliminated.

The manifestations induced by the administration of gonadal hormones in males or females, like those observed in individuals of either sex with hormone-producing tumors of the gonad or in males in whom testicular activity is stimulated by the use of chorionic gonadotropin, are evidence that to a marked degree exogenous androgenic hormones, and to a lesser degree exogenous estrogenic hormones, have a stimulating effect upon the growth of protein and osseous tissues. The findings in man are supported by numerous observations in a variety of animal species that androgens and/or estrogens under most circumstances have anabolic effects on protein and osseous tissues.[123,142-144]

3) *Conclusion from Observations*

The evidence indicates, therefore, that androgenic and estrogenic hormones (whether endogenous in origin or administered) have favorable effects on protein and osseous tissues characterized by an acceleration in protein deposition and an increase in bone anabolism. At present, the most potent and most practical preparation that is available for therapy is the combination of androgen with estrogen.

B. Interpretation of Mechanism

As was discussed previously, the protein and osseous tissues of the healthy adult individual are maintained in a state of dynamic equilibrium (Fig. 9, A). An increase in the total mass of protein or osseous tissues could be brought about by one of three mechanisms: (1) the rate of anabolism could be increased without a change in the rate of catabolism (Fig. 9, B); (2) the rate of catabolism could be decreased without a change in the rate of anabolism (Fig. 9, C); or (3) the total mass could be increased by a combination of a decrease in the rate of catabolism and an increase in the rate of anabolism (Fig. 9, D).

The author favors the interpretation that under most circumstances androgenic and estrogenic hormones have an anabolic rather than an anticatabolic effect on protein and osseous tissues.

Two pieces of evidence are cited:

(1) Both androgenic and estrogenic hormones cause an acceleration in the rate of bone growth and skeletal maturation in hypogonadal individuals.[110,111,127,132] *If gonadal hormones were anticatabolic, the rate of skeletal growth would not be increased; cessation of catabolism cannot accelerate bone anabolism.*

(2) The administration of androgen decreased the excretion of radioactive nitrogen from ingested labeled amino acids to the level of normal subjects in a patient with Cushing's syndrome who was excreting approximately twice the normal amount.[53] *If androgenic hormone was anticatabolic, it would have no effect on the amounts of ingested amino acids that are not utilized for protein synthesis, and hence are available for degradation and excretion.*

POINT 3: *The Effects of Anabolic Steroids in Combination with Corticoid Hormones Upon Protein and Osseous Tissues*

A. Observations

According to the interpretation that has been presented, corticoid hormones have an anti-anabolic effect on protein and osseous tissues, and androgenic and/or estrogenic hormones have an anabolic effect on protein and osseous tissues. It was postulated, therefore, that anabolic steroids would counteract the adverse effects of corticoid hormones on these tissues.[11]

1) *Combined with Endogenous Corticoids*

A number of studies have been reported which provide substantial evidence that this concept is correct. The administration of androgenic compounds to patients with Cushing's syndrome has resulted in clinical improvement, characterized by an increase in the thickness of the skin with a decrease in redness and in the purplish color of the striae, by a reduction in bruising, by a lessening of weakness, and by an increase in the muscle mass.[2,9,11,12,125,133-135,137,145-150] Similar but less pronounced clinical benefit has been observed in such patients following treatment with estrogenic hormones.[125,135,137,151-156] In patients with Cushing's syndrome, it has been demonstrated by metabolic balance studies

that under the influence of androgenic steroids alone, estrogenic steroids alone, and both anabolic agents together there is a retention of nitrogen, phosphorus, potassium, and sulfur in the proportions that are present in protein tissues, and likewise a retention of calcium and additional phosphorus in the proportions that are present in bone.[1,2,10-12,53,123,125,126,133-135,145,156] These anabolic effects on protein and osseous tissues have been induced without reducing the other manifestations of excessive corticoid hormone activity.[1,9-12,53,145,146,154-156]

The effect of androgen alone and in combination with estrogen upon the nitrogen, potassium, phosphorus, and sulfur balances in a patient with Cushing's syndrome is illustrated in figure 10. Note that these hormonal preparations induced a retention of over 3 Gm. of nitrogen per day, and simultaneously of sufficient quantities of potassium, of phosphorus, and of sulfur to approximate their proportions in muscle protoplasm for this amount of retained nitrogen.

Although patients with Cushing's syndrome excrete approximately twice the normal amount of radioactive nitrogen from ingested labeled amino acids, the administration of androgen reduced the excretion to the normal level.[53] This study indicates clearly that the anabolic steroid caused larger amounts of the ingested amino acids to be utilized for protein synthesis and hence reduced the amounts available for degradation and excretion.

2) *Combined with Administered Corticoids*

It has been pointed out that patients with a variety of clinical conditions now are being maintained on continuous corticoid therapy for months or even years, and that many of these individuals exhibit the manifestations of protein depletion and osteoporosis.[1-4,6,10,13,15-34] Thus far, anabolic steroids have been employed infrequently and then only for relatively short periods of administration in such patients. These periods of anabolic steroid therapy have been of sufficient length, however, to demonstrate that the simultaneous administration of these anabolic steroids with corticoid hormones does not interfere with the beneficial effects of the latter substances on the underlying disease.[1,2,13,16-18,25,27,33,36,158-161]

The effect of corticoid therapy alone and in combination with androgen upon the urinary calcium excretion of an elderly man with bronchial asthma and osteoporosis is illustrated in figure 11. Note that the administration of androgen to this patient after he had been receiving corticoid medication for some months reduced the excessive urinary calcium excretion to the normal range without interfering with the control of the asthmatic condition that had been achieved by the use of the corticoid substances.

In a number of patients with various disorders, it has been demonstrated by metabolic balance studies that the simultaneous administration of anabolic steroids (androgen and/or estrogen) with corticoid hormones decreased or eliminated the losses of nitrogen and calcium that were induced by the corticoid medications alone.[3,36]

The effect of adrenocorticotropic hormone (ACTH) alone, and in combination with androgen, upon the urinary nitrogen excretion of a woman with ovarian agenesis is illustrated in figure 12. Note that when ACTH and methyl testosterone are given simultaneously, the excessive nitrogen excretion that occurs with the ACTH alone is completely eliminated. The effect of cortisone acetate alone, and in combination with androgen, upon the nitrogen balance of a man with chronic lymphatic leukemia is illustrated in figure 13. Note that when the testosterone is administered simultaneously with cortisone acetate, the markedly negative nitrogen balance that was induced by the corticoid therapy is at first reduced to a moderately negative balance, and then replaced by a moderately positive nitrogen balance which persists even after the dosage of cortisone acetate is doubled.

Studies have been initiated recently on the effectiveness of androgen and estrogen in combination (the most potent and most practical anabolic steroid preparation that is available) in patients on chronic corticoid medication. In these studies, the efficacy of the anabolic steroids is being evaluated by two approaches: (1) as therapy to correct the protein depletion and osteoporosis that have been induced in patients by the chronic administration of corticoid agents; and (2) as therapy to prevent the adverse effects of corticoid substances on protein and osseous tissues in patients who are starting to receive continuous corticoid treatment. Although the final results of these investigations will not be available for several years, preliminary observations suggest that anabolic steroids are as beneficial in patients with an induced hyperadrenocorticism as they are in patients with an endogenous excess of adrenal cortical hormones.

3) *Conclusion from Observations*

The evidence indicates, therefore, that anabolic steroids counteract the adverse effects of endogenous corticoid hormones upon the protein and osseous tissues, and suggests that anabolic steroids probably have the same beneficial action on these unfavorable effects of administered corticoid substances.

B. Interpretation of Mechanism

It has been pointed out earlier in this presentation that on the basis of the available data the author favors the interpretation that corticoid hormones have an anti-anabolic and gonadal steroids have an anabolic effect on protein and osseous tissues. Hence, the beneficial action that arises from the simultaneous administration of anabolic steroids with corticoid substances is simply the result (Fig. 14) of the overcoming of the deleterious effects of the corticoid substances by the favorable effects of the anabolic steroids in the opposite direction.[36]

Clinical Implications

IMPLICATION 1: *For Pathologic Physiology and Mechanisms of Disease*

A. Endogenous Excess of Corticoids

It has been pointed out that protein and osseous tissues are in a state of dynamic equilibrium in the normal adult individual. Since the normal adult person is constantly producing from endogenous sources both anabolic steroids and anti-anabolic steroids, the amounts of these two types of hormones must be maintained in a state of balance in order that a dynamic equilibrium can exist (Fig. 15, A). An excess of corticoid steroids over anabolic steroids will lead to an inhibition of tissue anabolism. Such a disturbance in the balance of these two opposing types of hormones can be produced endogenously either by an absolute increase in the amount of corticoid materials without a change in the amount of anabolic steroids, or by a relative increase in the amount of corticoid materials because of a decrease in the amount of anabolic steroids.

1) *Absolute Excess*

a) *Cushing's Syndrome.* The excessive production of corticoid steroids by the adrenal cortex produces the clinical manifestations of Cushing's syndrome.[9,11,12] Many women with this disorder have amenorrhea. This may be due to the lack of gonadotropic hormone production by a protein-starved pituitary gland. However, the urinary gonadotropic hormone excretion has been normal in some patients with this disease, and high in several who were past the menopause. There is frequently, but not always, a compensatory increase in the androgenic hormones of the adrenal cortex so that the 17-ketosteroid excretion is increased. Furthermore, the increase in 17-ketosteroid excretion can be attributed in part to the fact that some of the metabolites of the corticosterone-type of adrenal cortical hormones are excreted as 17-ketosteroids. If one takes into consideration the debility of these patients, the level is almost always above what one would expect.[162] In spite of this attempt at compensation, the level of anabolic steroids is almost always inadequate for the quantity of cortical steroids that is being produced (Fig. 15, B), and the adverse effects of these latter substances upon the protein and osseous tissues appear.

2) *Relative Excess*

a) *The Normal Child.* The normal child has a level of anabolic steroids that is low for a mature individual but has an adult amount of cortical steroids[157,163,164] (Fig. 15, D). The adverse effects of the relative excess of corticoid materials do not occur, however, presumably because the normal child also has a considerable production of anterior pituitary growth hormone, which is an anabolic agent. At the same time, it is of interest to note the rather high incidence of spontaneous fracture in children on chronic corticoid therapy (Table 1 and Fig. 1). This finding may indicate that growth hormone in physiologic amounts is less effective than anabolic steroids of gonadal origin in countering and controlling the adverse effects of corticoid hormones upon the protein and osseous tissues. Such an interpretation would explain the apparently increased susceptibility of children to the unfavorable effects of corticoid therapy.

b) *Old Age.* The production of androgen and estrogen diminishes in both sexes with declining years.[157,165,166] The decrease in the endogenous gonadal hormone levels usually is gradual in men, and more rapid in women in whom the marked reduction of ovarian function at the time of the menopause creates an available level of circulating gonadal hormones well below that of the mature adult in her prime.[134] The reduced level of anabolic steroids in older persons may be by itself one of the important factors in the development of the depletion of protein and osseous tissues which is indicated by such manifestations as thin skin, wasted muscles, and atrophied (osteoporotic) bones. In contrast to the anabolic steroid production, the cortical steroid

production by the adrenal cortex appears to decrease very little in old persons of either sex.[134,163,167] Thus, the aging individual gradually develops a relative excess of endogenous corticoid hormones as his endogenous anabolic steroids decrease; his hormone imbalance, therefore, becomes qualitatively that of Cushing's syndrome (Fig. 15, E). The relative excess of anti-anabolic steroids may be another important factor in the development of protein tissue depletion and osteoporosis. This interpretation receives support from the recent studies of Sobel and Marmorston.[52,168-170] These investigators showed that in rats the ratio of the mucopolysaccharide constituent, hexosamine, to collagen in the skin and the bones is decreased with age, is decreased in young adult rats by the administration of cortisone acetate, and is maintained at the ratio of the young adult rat in aging animals by the administration of an anabolic steroid such as testosterone.

c) *The Postmenopausal Woman.* The decrease in the level of circulating gonadal hormones that occurs at the time of the menopause in women[157,165,166] has been mentioned. This creates a relative excess of anti-anabolic steroids (Fig. 15, F), since the cortical steroid production by the adrenal cortex appears to decrease very little with age.[134,163,167] Both the relative lack of anabolic steroids and the relative excess of cortical steroids may be factors in the development of protein tissue depletion and osteoporosis in the postmenopausal woman.

d) *Hypogonadism Associated with Normal Adrenal Cortical Function.* Loss or absence of anabolic gonadal hormones in males or females who have reached the chronologic age of young adults and who have normally functioning adrenal cortical glands results in a relative excess of cortical steroids (Fig. 15, G). As in old age and in the postmenopausal state, both the relative lack of anabolic steroids and the relative excess of anti-anabolic steroids may be factors in the development of protein tissue depletion and osteoporosis. In general, the younger these patients are, the longer it takes for the disturbance in tissue anabolism to become manifest.

B. Exogenous Excess of Corticoids

1) *Corticoid Therapy*

The administration of corticoid medication in sufficient amounts results in an excess of cortical steroids, and consequently, in an imbalance between the endogenous levels of anabolic hormones and of anti-anabolic steroids. The excess of cortical steroids inhibits tissue anabolism, which leads to protein depletion and osteoporosis if the inhibition is continued for a sufficient time. The larger the dosage of corticoid materials (that is, the greater the excess of anti-anabolic steroids over anabolic hormones), the greater the inhibition of anabolism, and the shorter the time before adverse effects appear. The endogenous ratio of anabolic to anti-anabolic hormones prior to the corticoid medication affects the susceptibility of the individual to the development of these unfavorable manifestations. This aspect is discussed in the next section.

In the person in whom the physiologic status of the protein and osseous structures has not been disturbed significantly by the tissue-affecting factors (mentioned below), an indication of the pre-existing endogenous anabolic to anti-anabolic ratio may be obtained from the dosage of corticoid substances and/or the period of continuous therapy that is tolerated by the patient before the adverse manifestations become apparent. Three different ratios are possible.

(1) *Excess of Anti-Anabolic Hormones.* In those individuals who develop adverse effects after a comparatively small amount and/or duration of corticoid therapy a relative excess of endogenous corticoid steroids may exist (as in children, in elderly persons, in postmenopausal women, and in patients of either sex with hypogonadism and normal adrenal cortical function).

(2) *Equilibrium of Anabolic and Anti-Anabolic Hormones.* In those individuals who develop adverse effects after a comparatively moderate amount and/or duration of corticoid therapy an equilibrium between the endogenous anabolic and corticoid steroids may exist (as in normal adults, and in patients with both gonadal and adrenal cortical insufficiency).

(3) *Excess of Anabolic Hormones.* In those individuals who develop adverse effects after a comparatively large amount and/or duration of corticoid therapy a relative or an absolute excess of endogenous anabolic hormones may exist [as in patients with adrenal cortical insufficiency and normal gonadal function, and in persons of either sex with hormone-producing tumors of the gonads (who have an excess of gonadal anabolic hormones), with the adrenogenital syndrome (who have an excess of adrenal anabolic steroids), or with acromegaly or gigantism (who have an excess of anterior pituitary anabolic [growth] hormone)].

2) *Susceptibility to Adverse Effects Upon Protein and Osseous Tissues*

Patients with a normal endogenous balance between anabolic and corticoid steroids are able to tolerate chronic corticoid therapy in considerable amounts and/or for prolonged periods of treatment before they develop the manifestations of adverse effects upon the protein and osseous tissues. Obviously, the susceptibility to protein depletion and osteoporosis is increased in those who prior to the chronic corticoid medication have had a relative excess of cortical steroids. This group includes the children, the elderly individuals, the postmenopausal women, and the patients of either sex with hypogonadism and normal adrenal cortical function. The susceptibility is increased also in those patients with hypogonadism combined with hypoadrenalism, who do not have sufficient quantities of endogenous anabolic steroids to offset even normal replacement amounts of corticoid medication. It should be noted that more than the adrenal steroid replacement dosage of cortical hormones must be administered before an anti-anabolic excess will be created in a patient with adrenal cortical insufficiency and *normal* gonadal hormone production. A patient with this disorder, therefore, has a decreased susceptibility to the development of adverse effects upon protein and osseous tissues as a result of corticoid medication. In contrast, a relatively small amount of cortical hormones will produce an excess of anti-anabolic steroids in a patient with adrenal cortical insufficiency and *reduced* gonadal hormone production (as in panhypopituitarism, or in Addison's disease with gonadal hypofunction). Thus, corticoid materials in "physiologic" amounts (which supply only enough hormone to restore the endogenous cortical steroid level to the normal range) in time may induce adverse effects upon the protein and osseous tissues in the patient who has both gonadal and adrenal cortical insufficiency. From the evidence that has been presented, it is obvious that in such a patient, anabolic steroids should be administered simultaneously with corticoid replacement therapy to eliminate the potential hazard.

The susceptibility to protein depletion and osteoporosis as a result of corticoid therapy is decreased in those patients who have an excess of an endogenous anabolic hormone. This group includes the patients of either sex with anabolic hormone-producing tumors of the gonads, the individuals with an excess of anabolic adrenal steroids (as in the adrenogenital syndrome), and the persons with an excess of the anabolic (growth) hormone of the anterior pituitary (as in acromegaly or gigantism). In patients with these disorders, a large amount of corticoid therapy must be administered before an anti-anabolic excess will be obtained. In the adrenogenital syndrome, intensive corticoid therapy effectively restores the endogenous balance between anti-anabolic and anabolic hormones through two mechanisms: by increasing the level of cortical steroids, and by suppressing the adrenal production of anabolic steroids. The clinical improvement of such patients following large amounts of corticoid hormones is striking.[171-175] In patients with hyperfunctioning tumors of the gonads, corticoid agents in large doses should be administered to reduce the manifestations of excessive anabolic activity until the lesion can be removed surgically or to control the excessive anabolism in those cases which are inoperable. In acromegaly or gigantism, large amounts of cortical steroids should be employed to diminish the excessive growth of protein and osseous tissues.

Factors which specifically alter the physiologic status of the protein and the osseous tissues also increase the susceptibility of patients to the unfavorable effects of corticoid therapy upon these tissues. These factors include: malnutrition, inadequate intake of protein and/or minerals during the corticoid therapy, disturbed gastrointestinal tract function with poor absorption of protein and/or minerals, pre-existing osteoporosis or other chronic systemic bone disease, marked restriction of physical activity or enforced bed rest during the corticoid therapy, chronic acidosis or other general or renal disorders with hypercalcuria, and similar conditions. Alterations which decrease the tissue responsiveness to corticoid hormones also probably occur, and thereby decrease the susceptibility of patients to the development of protein depletion and osteoporosis as a consequence of corticoid medication.

IMPLICATION 2. *For Therapy with Anabolic Steroids*

A. Indications for Therapeutic Use

Anabolic steroids should be administered as therapy to restore the protein and osseous

tissues in patients who have protein depletion and/or osteoporosis associated with Cushing's syndrome, old age, the postmenopausal state, hypogonadism with normal adrenal cortical function, and chronic corticoid therapy. The anabolic steroids should be administered in adequate amounts and for a sufficient time to correct the protein depletion and osteoporosis. Although adrenalectomy is the main therapeutic procedure for persistent and/or severe Cushing's syndrome, anabolic steroids are indicated preoperatively to protect the tissues from further depletion and to initiate the restorative processes; after operation, such patients should be placed upon anabolic steroid therapy at least until the adverse effects upon protein and osseous tissues are eliminated. Attention is called to the point that anabolic steroids should not be administered to those patients with Cushing's syndrome who have a malignant adrenal cortical tumor, since the anabolic steroids may stimulate the growth of the neoplastic lesion.

B. Indications for Preventive Use

The most important indication that arises from the evidence that has been surveyed is to administer anabolic steroids as therapy to prevent the adverse effects upon the protein and osseous tissues in patients who are being started on a regimen of chronic corticoid medication. The anabolic steroids should be administered in adequate amounts for as long as the corticoid materials are given. This indication for the use of anabolic steroids applies also to patients with adrenal cortical insufficiency and hypogonadism who are being given minimal doses of corticoid agents as replacement therapy, since these individuals lack sufficient endogenous anabolic steroids to offset the adverse effects of corticoid hormones even when only the normal endogenous levels of the latter are present. Furthermore, the evidence in this presentation provides strong support for the contention that to prevent the development of protein depletion and osteoporosis, anabolic steroids should be administered to all persons who have passed the prime of life and are becoming elderly, to all women at and after the time of the menopause, and to patients with hypogonadism and normal adrenal cortical function.

C. Regulation of Dosage

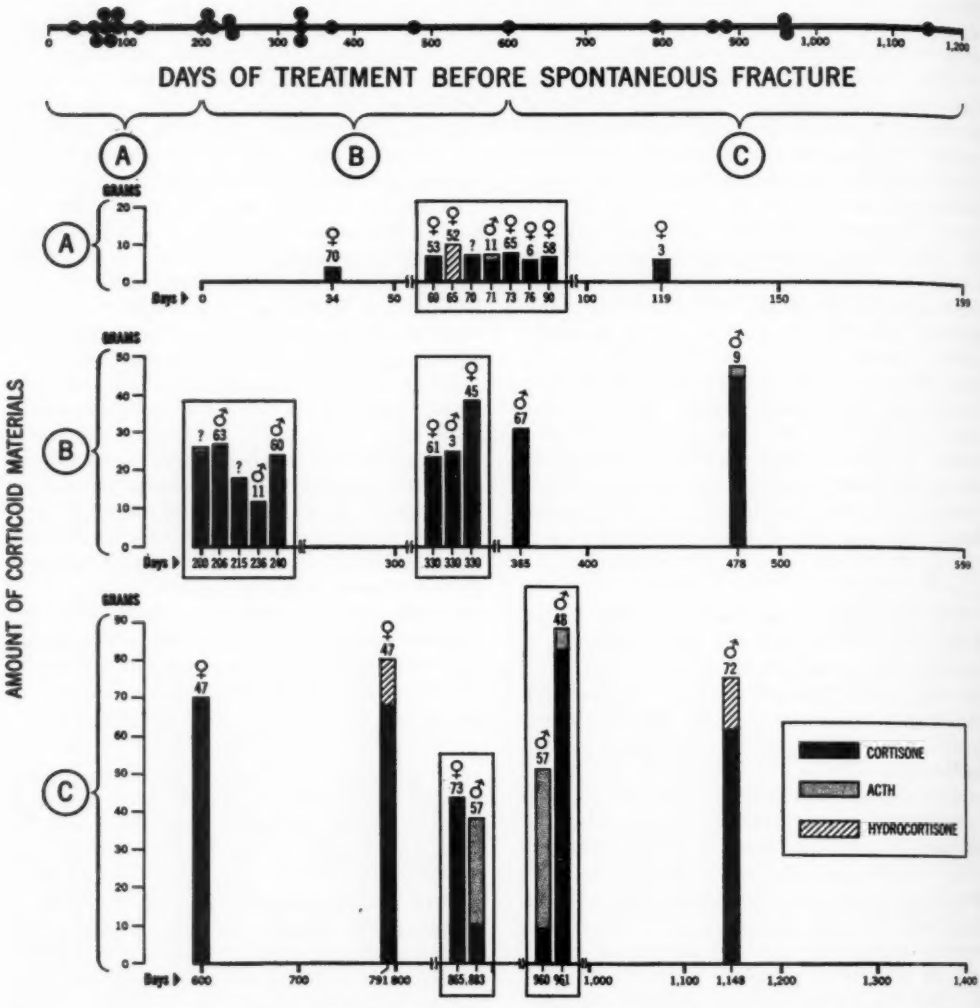
The adequacy of the anabolic steroid dosage in patients who also are receiving chronic corticoid therapy can be determined in most cases by repeatedly examining the urine for hypercalcuria (which indicates an adverse corticoid hormone effect upon bone). A rough estimate of the calcium content of the urine can be obtained by the use of the Sulkowitch test.[176] The amounts of the anabolic compounds that are administered should be increased until the urinary calcium excretion falls to the normal range. The urinary calcium level should be maintained in this range throughout the corticoid regimen by adjusting the anabolic steroid dosage from time to time. In addition, by the use of a diet in which the total caloric intake is maintained at a level which approximates the requirements of the patient through the administration of adequate amounts of fat and protein with a minimal intake of carbohydrate, the anti-anabolic effects of cortical hormones upon the protein and osseous tissues may be reduced.[177] When anabolic steroids are employed as preventive therapy, the dosage should be adjusted to maintain the patient in an optimal clinical state. Prolonged treatment will be required, since the underlying endogenous imbalance between anabolic and anti-anabolic steroids is still present whenever the anabolic steroid therapy is discontinued.

D. Practical Therapy

At present, the combination of androgen with estrogen provides the most potent and most practical anabolic preparation that is available for therapy. Such a combination has the advantages of: (1) adding the more marked osseous-anabolic effect of the estrogen to the more marked protein-anabolic effect of the androgen, and (2) reducing the undesirable actions of either hormone alone upon the genital organs and the accessory sexual structures. The preparation recently introduced as Deladumone* (90 mg. of testosterone enanthate and 4 mg. of estradiol valerate dissolved in each milliliter of sesame oil) seems to meet the requirements for anabolic steroid therapy very satisfactorily. It has a potent anabolic effect that is sustained for 3 to 4 weeks after a single intramuscular injection of 1 to 2 cc., and it appears to have an optimal androgen-to-estrogen ratio that results in undesirable masculinizing or feminizing actions in only a very small percentage of patients of either sex.

*Made by E. R. Squibb and Sons Division, Olin Mathieson Chemical Corporation, New York, N. Y.

FIG. 1

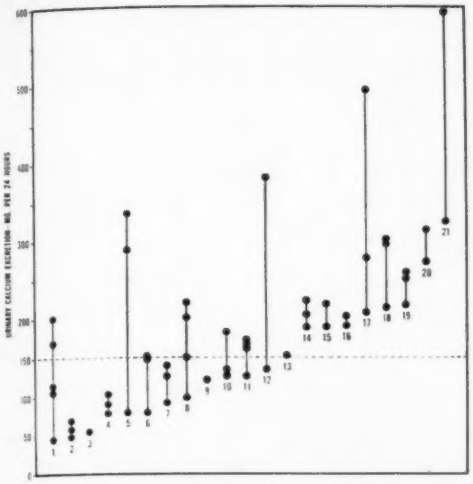


The Amount and the Duration of Corticoid Therapy Prior to the Occurrence of Spontaneous Fractures in 26 Patients with Various Disorders.

The scale for the total amount in grams of corticoid materials [cortisone, hydrocortisone, and adrenocorticotropic hormone (ACTH)] administered prior to the occurrence of spontaneous fracture is given as the ordinate; the scale for the duration in days of corticoid therapy prior to the occurrence of spontaneous fracture is given as the abscissa. Note that there are four different time scales (top, A, B, and C) and that the five areas enclosed in rectangles are enlarged horizontally but not vertically. Cortisone therapy is shown as a black bar; adrenocorticotropic hormone (ACTH) therapy as a white bar; and hydrocortisone therapy as a hatched bar. The sex and the age of the patient is given over each column of therapy.

The figure has four divisions: Top—the distribution of spontaneous fractures in relation to duration of treatment on a continuous time scale; A—the amount of medication and the occurrence of spontaneous fractures during therapy from 0 to 199 days; B—the amount of medication and the occurrence of spontaneous fractures during corticoid therapy from 200 to 599 days; and C—the amount of medication and the occurrence of spontaneous fractures from 600 to 1,400 days. It will be seen that the occurrence of spontaneous fractures is related to both the amount and the duration of therapy with corticoid materials; and that spontaneous fractures may result from treatment with cortisone, hydrocortisone, or ACTH. These findings are evidence that corticoid therapy in some patients has an adverse effect on osseous tissue. For additional data on these patients, see tables 1 and 2. (For further discussion, see text.)

FIG. 2



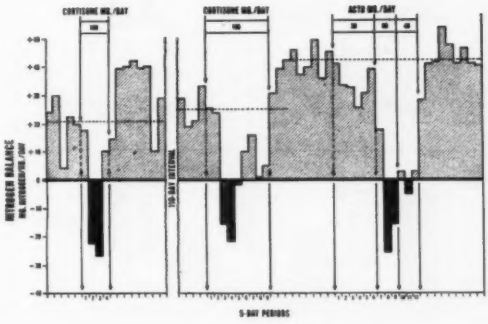
The Urinary Calcium Excretion of 21 Patients with Asthma on Prolonged Cortisone Therapy.

The scale for the urinary calcium excretion in milligrams per 24 hours is given as the ordinate; the individual patients are numbered consecutively in order of increasing calcium excretion along the abscissa. Each black dot represents a single determination of the urinary calcium excreted per 24 hours; all determinations for an individual patient are connected by a vertical line. The horizontal line of dashes at 150 mg. represents the level of excretion per 24 hours which usually is maximal for normal subjects. Each patient required at least 600 mg. of cortisone to become cleared of asthma, and from 50 to 150 mg. of cortisone each day to be maintained in a symptom-free state. In most patients, the cortisone was administered intramuscularly. The calcium determinations were made when the patients were on a maintenance regimen. The amount of cortisone therapy administered prior to each calcium determination, and the order of and interval between repeated determinations on the same patient are not stated by the authors.

It will be seen that two-thirds of the patients had at least one elevated urinary calcium value, and that over one-third had all of their urinary calcium excretion values above the normal maximal level. More than half of the determinations gave values in the hypercalcuric range. These findings are evidence that corticoid therapy in some patients has an adverse effect on osseous tissue.

(For further discussion, see text. Data recharted from *Figure 4* in Irwin, Henneman, Wang, and Burrage,[13] and reproduced with the permission of the authors and the *J. Allergy.*)

FIG. 3



The Effect of Corticoid Hormones upon the Nitrogen Balance of an Elderly Man.

This metabolic balance study on a 74 year old man with osteoporosis (M.A.) consists of 60 five-day periods. The scale for the nitrogen balance in milligrams of nitrogen per kilogram per day is given as the ordinate; the scale of the five-day periods is given as the abscissa. The horizontal line starting at zero on the ordinate is the baseline of the balance; balances extending from the baseline toward the top of the diagram are positive; those extending from the baseline toward the bottom of the diagram are negative; positive balances are represented by hatched areas; negative balances by black areas. The horizontal dotted lines represent the approximate levels of the balances during the control periods. Cortisone and adrenocorticotropic hormone (ACTH) were administered intramuscularly each day during the periods indicated. The chart is interrupted for an interval of 110 days during which other non-pertinent studies were carried out.

It will be seen that the positive nitrogen balance is reduced and becomes negative each time a sufficient amount of either cortisone or ACTH is administered. The effect of the corticoid agents upon the nitrogen balance is apparent in 5 to 10 days after the start of the medication, and tends to become less pronounced as the therapy is continued for longer than 20 days. Following the cessation of the corticoid medication, the nitrogen balance shows a "rebound" to a positive balance that is greater than that of the control periods. These findings are evidence that corticoid therapy had an adverse effect on protein tissue.

(For further discussion, see text. Data recharted from *Figure 3* in Kountz, Ackermann, and Kheim,[35] and reproduced with the permission of the authors and the *J. Clin. Endocrinol. and Metabol.* Additional data on this patient are published elsewhere [*Case No. 8* in Ackermann and Toro[38]]).

FIG. 4

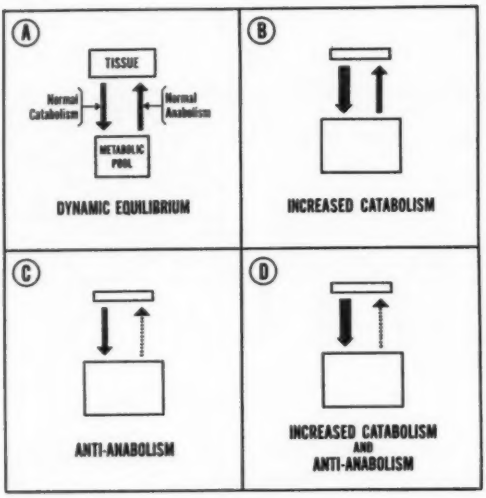


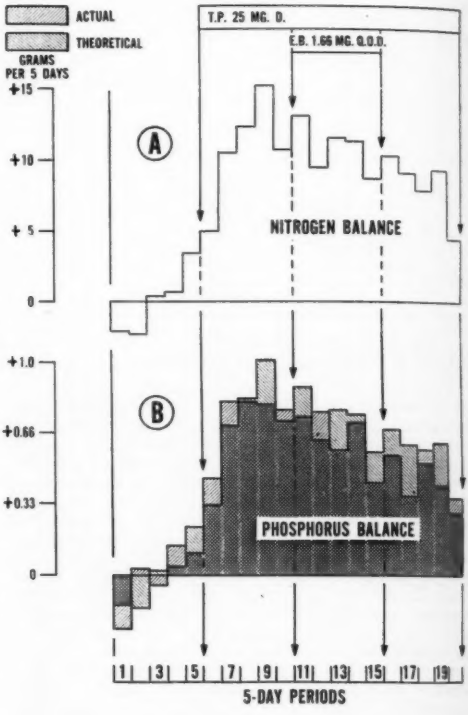
Diagram Illustrating Three Possible Mechanisms Leading to Decreased Total Mass of Protein or Osseous Tissues.

The rectangles represent the tissues (protein or osseous) and the metabolic pool; the size of the rectangles represents the total quantity of the mass of protein or osseous tissues and the total quantity of material in the metabolic pool; the arrows represent the metabolic processes, anabolism and catabolism; and the size of the arrows represents the rates of these metabolic processes.

The diagram has four divisions: A—the normal total mass of protein or osseous tissues that results from the dynamic equilibrium between these tissues and the metabolic pool when the rates of anabolism and catabolism are both normal; B—the decreased total mass of protein or osseous tissues that results when the rate of anabolism is normal and the rate of catabolism is increased; C—the decreased total mass of protein or osseous tissues that results when the rate of anabolism is decreased and the rate of catabolism is normal; and D—the decreased total mass of protein or osseous tissues that results when both the rate of anabolism is decreased and the rate of catabolism is increased. It will be seen that a decreased total mass of protein or osseous tissues can be produced by any one of the three mechanisms that are depicted in divisions B, C, or D. (For further discussion, see text.)

This metabolic balance study (Fig. 5) on a 72 year old man with osteoporosis (M.H., M.G.H. 267511) consists of 20 five-day periods. The scales for the balances in grams per 5-day period are given as the ordinates; the scale of the 5-day periods is given as the abscissa. The horizontal line starting at zero on each ordinate is the baseline of that particular balance; balances extending from the baselines toward the tops of the diagrams are positive; those extending from the baselines toward the bottoms of the diagrams are negative. The balances are charted as deviations from the average of the control periods rather than as the balances actually measured. The scales are chosen so that one unit of phosphorus is equal to 15 units of nitrogen to express the constant interrelationship of these substances that exists in normal protein tissues; thus, the charted area of the phosphorus balance (after the phosphorus theoretically retained with calcium has been subtracted) should equal the charted area of the nitrogen balance when protein tissues have been retained. The factors for the calculations are given in *Table 8* in Albright and Reifenstein;[135] the methods for the accumulation, presentation, and interpretation of these data are discussed in detail in Reifenstein, Albright, and Wells.[126] T.P. = testosterone propionate; E.B. = estradiol benzoate; D. = dosage per day; Q.O.D. = dosage every other day. Testosterone propionate and estradiol benzoate were administered intramuscularly during the periods indicated.

FIG. 5

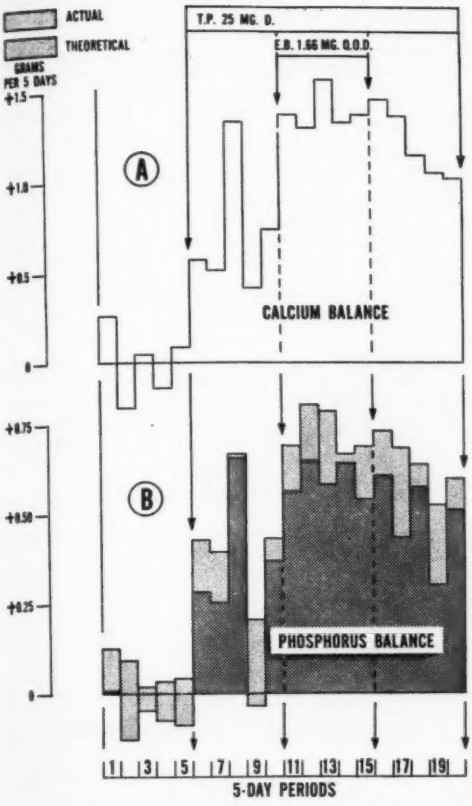


A Comparison of the Deviations in the Nitrogen and the Phosphorus Balances as a Result of Androgen Alone and of Androgen Combined with Estrogen in an Elderly Man.

The figure has two divisions: A—the measured nitrogen balance, and B—the measured nitrogen balance with superimposed theoretical nitrogen balance explainable by the measured phosphorus balance (after the phosphorus theoretically retained with calcium has been subtracted). It will be seen that there is a close correspondence between the measured and the theoretical nitrogen balances. This is evidence that testosterone propionate alone and in combination with estradiol benzoate induced a retention of nitrogen and phosphorus in the proportions that exist in muscle protoplasm. For an additional analysis on this patient, see figure 6.

(For further discussion, see text. Data recharted from *Case 6* in Reifenstein and Albright,[125] and reproduced with the permission of the authors and the *J. Clin. Invest.* Additional data on this patient are published elsewhere [Reifenstein, Albright, Parson, and Bloomberg;[136] Albright;[12, 133, 134] Reifenstein, Albright, and Wells;[126] and *Case 13 (Figs. 78 and 155)* in Albright and Reifenstein[135].)

FIG. 6



A Comparison of the Deviations in the Calcium and the Phosphorus Balances as a Result of Androgen Alone and of Androgen Combined with Estrogen in an Elderly Man.

This metabolic balance study on a 72 year old man with osteoporosis (M.H., M.G.H. 267511) consists of 20 five-day periods. The method of charting these data is described in the legend to figure 5. In this chart, the scales are chosen so that one unit of phosphorus is equal to two units of calcium to express the constant interrelationship of these substances that exists in normal osseous tissues; thus, the charted area of the phosphorus balance (after the phosphorus theoretically retained with nitrogen has been subtracted) should equal the charted area of the calcium balance when osseous tissues have been retained. The factors for the calculations are given in *Table 8* in Albright and Reifenstein;[135] the methods for the accumulation, presentation, and interpretation of these data are discussed in detail in Reifenstein, Albright, and Wells.[126]

The figure has two divisions: A—the measured calcium balance, and B—the measured calcium balance with superimposed theoretical calcium balance explainable by the measured phosphorus balance (after the phosphorus theoretically retained with nitrogen has been subtracted). It will be seen that there is a close correspondence between the measured and the theoretical calcium balance. This is evidence that testosterone propionate alone and in combination with estradiol benzoate induced a retention of calcium and phosphorus in the proportions that exist in bone. For an additional analysis on this patient, see figure 5.

(For further discussion, see text. Data recharted from *Case 6* in Reifenstein and Albright,[125] and reproduced with permission of the authors and the *J. Clin. Invest.* Additional data on this patient are published elsewhere [Reifenstein, Albright, Parson, and Bloomberg;[136] Albright;[12, 133, 134] Reifenstein, Albright, and Wells;[126] and *Case 13 (Figs. 78 and 155)* in Albright and Reifenstein[135].)

FIG. 7

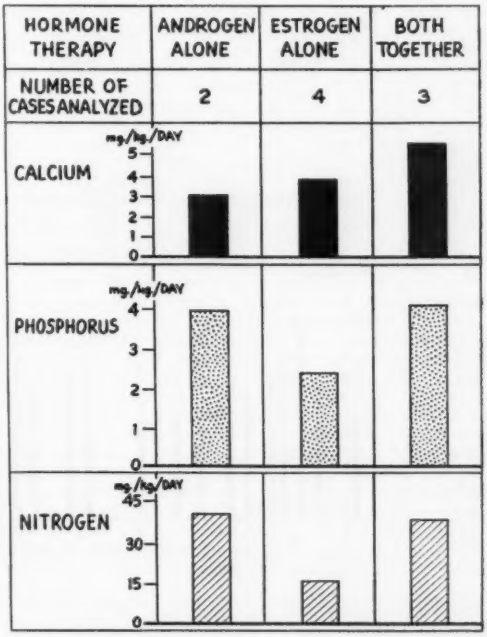


Chart Illustrating the Average Net Retention of Calcium, Phosphorus, and Nitrogen with Prolonged Androgenic Therapy Alone, with Estrogenic Therapy Alone, and with Androgenic and Estrogenic Therapy in Combination, in Patients with Postmenopausal and/or Senile Osteoporosis during Metabolic Balance Studies.

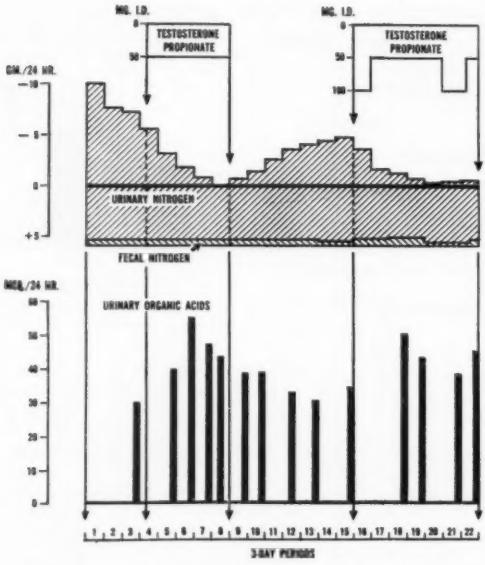
The scales for the average net retention in milligrams per kilogram per day are given as the ordinates; the results for 2 patients on androgen alone, for 4 patients on estrogen alone, and for 3 patients on both hormones together are given on the abscissa. The periods of analysis during therapy ranged from 24 to 72 days. The data for the first 5 days after the start of therapy were omitted from the calculations to eliminate the transitional period of adjustment to the therapeutic regimen. The scales are chosen so that one unit of phosphorus is equal to two units of calcium and 15 units of nitrogen to express the constant interrelationships of these substances that exist in normal protein and osseous tissues; thus, the height of the phosphorus column should equal the sum of the columns for nitrogen and calcium when protein and osseous tissues have been retained. The factors for the calculations are given in *Table 8* in Albright and Reifenstein;[135] the methods for the accumulation, presentation, and interpretation of these data are discussed in detail in Reifenstein, Albright, and Wells.[126]

It will be seen that, when estrogen is given alone, there is a greater retention of calcium and a lesser retention of nitrogen than when androgen is given alone. Note further that, while the combination of both gonadal hormones does not result in a significantly greater nitrogen retention than is obtained with androgen alone, the combination results in a greater calcium retention than with either estrogen or androgen alone. These findings are evidence that

androgen and estrogen have qualitatively identical but quantitatively different somatotropic effects on protein and osseous tissues.

(For further discussion, see text. [From Reifenstein[137].)

FIG. 8



The Effect of Androgen upon the Nitrogen Balance and the Urinary Organic Acid Excretion of an Obese Man on a Low Protein and Low Caloric Intake.

This metabolic balance study on a 42 year old man with obesity (173 kg.; 380 lb.) (C.U., M.G.H. 102331) consists of 22 three-day periods. The scale for the nitrogen balance in grams per 24 hours and the scale for the urinary excretion of organic acids in milliequivalents per 24 hours are given as the ordinates; the scale of the 3-day periods is given as the abscissa. The horizontal line starting at zero on the ordinate scale for the nitrogen balance is the baseline of this balance; the intake is charted from this baseline to the bottom of the nitrogen diagram; the fecal nitrogen excretion is charted from the bottom line of the nitrogen diagram toward the top of the figure; the urinary nitrogen excretion is charted from top of the fecal excretion toward the top of the figure. Where the total excretion exceeds the baseline, the patient is in negative nitrogen balance; where the total excretion approximates the baseline, the patient is in nitrogen equilibrium. During the balance study, the patient was on a constant intake per 24 hours of 6.5 Gm. of nitrogen and 342 calories. I.D. = intramuscularly each day.

It will be seen that during the control periods the patient is in a markedly negative nitrogen balance, and that during the administration of testosterone propionate the urinary nitrogen excretion falls progressively until the patient is in nitrogen equilibrium; at the same time there is a rise in the urinary organic acid excretion. Following the cessation of the testosterone propionate therapy the urinary nitrogen increases until the patient again is in a markedly negative nitrogen balance; at the same time the urinary organic acid excretion falls to the pre-treatment level. The second administration of testosterone propionate again restores the nitrogen balance to equilibrium and increases the urinary organic acid excretion. This study is evidence that testosterone propionate has a marked anabolic effect upon protein tissues even in a patient on a low protein and inadequate caloric intake who has been utilizing tissue proteins for energy. The increased excretion of organic acids during the administration of testosterone propionate in this study is an indication of increased combustion of fat for energy. During the 66 days of study there was a loss of 56 pounds of weight; 43 pounds during the 31 days when the patient was not receiving medication, and only 13 pounds during the 35 days when he was being given testosterone propionate. Since fat tissue weighs only 108 grams per 1,000 calories while protein tissue weighs 1,248 grams per 1,000 calories,[12] the decrease in the rate of weight loss during the treatment periods also is an indication of the increased combustion of fat during the administration of testosterone propionate.

(For further discussion, see text. Data recharted from Albright, Reifenstein, and Forbes,[139] and reproduced with permission of the authors and the Transactions of the Macy Conference [October 8-9, 1943] on Metabolic Aspects of Convalescence, Including Bone and Wound Healing.)

FIG. 9

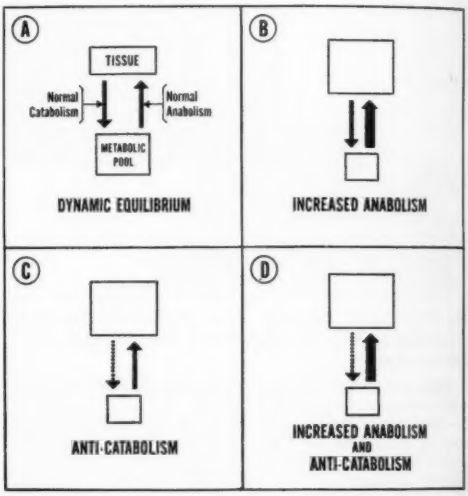
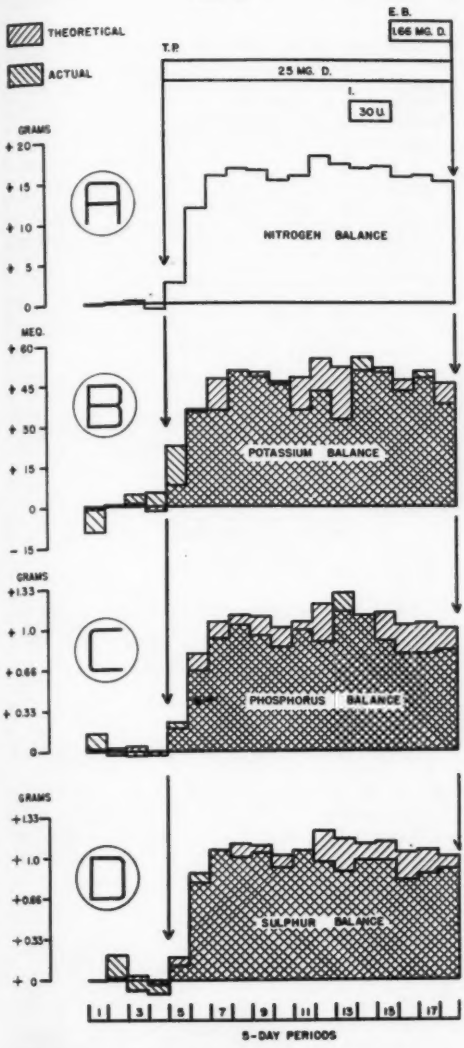


Diagram Illustrating Three Possible Mechanisms Leading to Increased Total Mass of Protein or Osseous Tissues.

The construction of the diagram is described in the legend to figure 4.

The diagram has four divisions: A—the normal total mass of protein or osseous tissues that results from the dynamic equilibrium between these tissues and the metabolic pool when the rates of anabolism and catabolism are both normal; B—the increased total mass of protein or osseous tissues that results when the rate of anabolism is increased and the rate of catabolism is normal; C—the increased total mass of protein or osseous tissues that results when the rate of anabolism is normal and the rate of catabolism is decreased; and D—the increased total mass of protein or osseous tissues that results when both the rate of anabolism is increased and the rate of catabolism is decreased. It will be seen that an increased total mass of protein or osseous tissues can be produced by any one of the three mechanisms that are depicted in divisions B, C, or D. (For further discussion, see text.)

FIG. 10



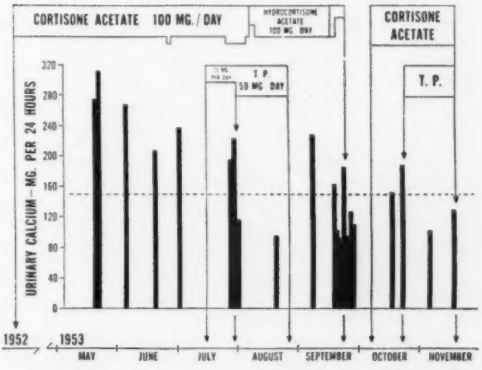
A Comparison of the Deviations in the Nitrogen, Potassium, Phosphorus, and Sulfur Balances as a Result of Androgen Alone and of Androgen Combined with Estrogen in a Woman with Cushing's Syndrome.

This metabolic balance study on a 25 year old woman with Cushing's syndrome and osteoporosis (B.V., M.G.H. 74372) consists of 18 five-day periods. The scales for the balances in amounts per 5-day period are given as the ordinates; the scale of the 5-day periods is given as the abscissa. The horizontal line starting at zero on each ordinate is the baseline of that particular balance; balances extending from the baseline toward the tops of the diagrams are positive; those extending from the baseline toward the bottoms of the diagrams are negative. The balances are charted as deviations from the average of the control periods rather than as the balances actually measured. The scales are chosen so that 15 units of nitrogen are equal to three units (in grams; 45 units in milliequivalents) of potassium, to one unit of phosphorus, and of one unit of sulfur to express the constant interrelationships that exist in normal protein tissues; thus, the charted areas of the potassium balance, of the phosphorus balance (after the phosphorus theoretically retained with calcium has been subtracted), and of the sulfur balance in each instance should equal the charted area of the nitrogen balance when protein tissues have been retained. The data for potassium are based on analyses of urinary excretions alone; the fecal potassium excretion was assumed to be 8 per cent of the potassium intake. The factors for the calculations are given in *Table 8* in Albright and Reifenstein;[135] the methods for the accumulation, presentation, and interpretation of these data are discussed in detail in Reifenstein, Albright, and Wells.[126] T.P. = testosterone propionate; E.B. = estradiol benzoate; I = insulin; D = dosage per day; U = units per day. Testosterone propionate, estradiol benzoate, and insulin were administered intramuscularly each day during the periods indicated.

The figure has four divisions: A—the measured nitrogen balance; B—the measured nitrogen balance with superimposed theoretical nitrogen balance explainable by the measured potassium balance; C—the measured nitrogen balance with superimposed theoretical nitrogen balance explainable by the measured phosphorus balance (after the phosphorus theoretically retained with calcium has been subtracted); and D—the measured nitrogen balance with superimposed theoretical nitrogen balance explainable by the measured sulfur balance. It will be seen that there is a close correspondence between the measured and the theoretical nitrogen balances. This is evidence that testosterone propionate therapy induced a retention of nitrogen, potassium, phosphorus, and sulfur in the proportions that exist in muscle protoplasm. Furthermore, the estradiol benzoate induced no significant alteration in retention when it was added to the testosterone propionate during periods 16, 17, and 18.

(For further discussion, see text. Data from Reifenstein, Albright, and Wells,[126] and reproduced with the permission of the authors and the *J. Clin. Endocrinol.* Additional data on this patient are published elsewhere [*Case 37* in Fraser, Forbes, Albright, Sulkowitch, and Reifenstein;[157] Albright;[12, 133, 134] *Case 1* in Albright, Parson, and Bloomberg;[11] *Case 10* in Reifenstein and Albright;[125] and *Case 15 (Figs. 82 and 156)* in Albright and Reifenstein[135].)

FIG. 11



The Effect of Corticoid Therapy Alone and in Combination with Androgen Upon the Urinary Calcium Excretion of an Elderly Man with Bronchial Asthma and Osteoporosis.

This study on a 60 year old man with bronchial asthma and osteoporosis (W.G., M.G.H. 447828) con-

sisted of observations over more than 18 months. The scale for the urinary calcium excretion in milligrams per 24 hours is given as the ordinate; the dates of treatment are given as the abscissa. The horizontal line of dashes at 150 mg. represents the level of excretion per 24 hours which usually is maximal for normal subjects. T.P. = testosterone propionate. Cortisone acetate and hydrocortisone acetate were administered orally or intramuscularly as indicated; testosterone propionate was administered intramuscularly as indicated.

It will be seen that the urinary calcium excretion was considerably elevated in May, June, and July 1953 after the patient had been on continuous cortisone therapy for approximately one year. Note that the calcium excretion fell to the normal range as soon as a sufficient amount (50 mg. per day) of testosterone propionate was administered along with the corticoid therapy; that the excretion became elevated again as soon as the androgenic hormone was omitted; and that the excretion returned to the normal range as soon as the corticoid therapy was reduced to low doses or omitted. This is evidence that the simultaneous administration of the anabolic steroid, testosterone propionate, eliminates and/or prevents the adverse effect of chronic corticoid therapy upon osseous tissue and calcium metabolism. Not indicated in the figure is the fact that the control of the asthmatic condition that had been achieved by the use of the corticoid substances was not interferred with by the simultaneous administration of the androgen.

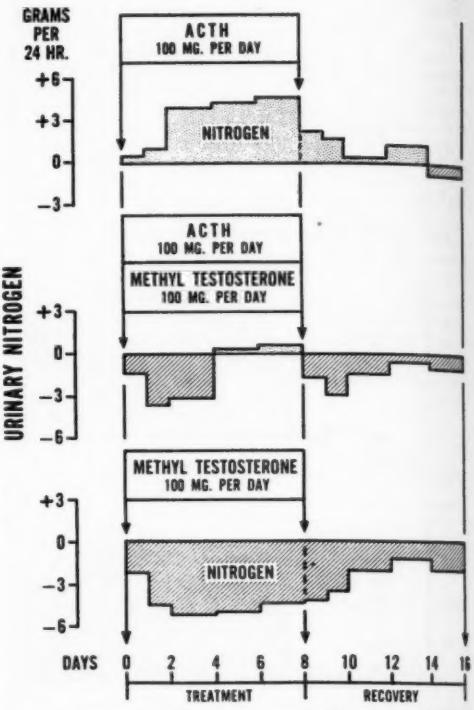
(For further discussion, see text. Data recharted from *Figure 3* in Irwin, Henneman, Wang, and Burrage,[13] and reproduced with the permission of the authors and the *J. Allergy*. Additional data on this patient are published elsewhere [Burrage, Ritchie, Mansmann, Irwin, and Russfield[25]].)

This metabolic balance evaluation (Fig. 12) on a 38 year old woman with ovarian agenesis (M.K.H., M.G.H. 144936) consists of three separate studies of 16 days each. The scales for the urinary nitrogen excretion in grams per 24 hours are given as the ordinate; the scale of the days of treatment and of recovery is given as the abscissa. The excretions are charted as deviations from the average of the control periods rather than as the excretions actually measured. An increase in the urinary nitrogen excretion is charted as a stippled area; a decrease as a hatched area. During the periods indicated, adrenocorticotropic hormone (ACTH) was administered intramuscularly daily in four equal doses; methyl testosterone orally daily in five equal doses.

It will be seen that ACTH alone caused a marked increase in the urinary nitrogen excretion, and that methyl testosterone alone caused a marked decrease in the urinary nitrogen excretion. When ACTH and methyl testosterone were given simultaneously, the effects upon the nitrogen excretion were partially neutralized during the first four days and completely eliminated during the last four days of the period of administration. This is evidence that the adverse effects of corticoid therapy on protein tissues can be reduced or prevented by the simultaneous administration of an anabolic steroid.

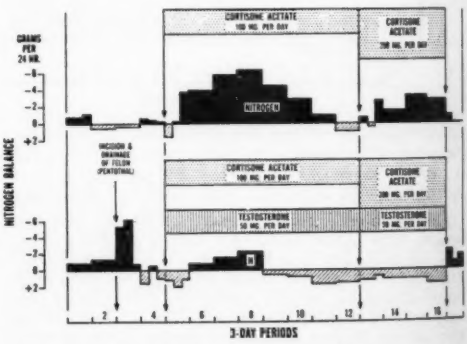
(For further discussion, see text. Data recharted from *Figures 4 and 6* in Bartter, Fourman, Albright, Jefferies, Dempsey, and Carroll,[36] and reproduced with the permission of the authors, of Pituitary-Adrenal Function, and of the American Association for the Advancement of Science. Additional data on this patient are published elsewhere [Bartter, Forbes, and Albright[39]].)

FIG. 12



The Effect of Adrenocorticotropic Hormone (ACTH) Alone, of Methyl Testosterone Alone, and of ACTH and Methyl Testosterone in Combination, Upon the Urinary Nitrogen Excretion of a Woman with Ovarian Agenesis.

FIG. 13


CORTISONE ACETATE 100 MG. PER DAY
CORTISONE ACETATE 200 MG. PER DAY
NITROGEN
INCISION & DRAINAGE OF FOLLICULAR
CORTISONE ACETATE 100 MG. PER DAY
CORTISONE ACETATE 200 MG. PER DAY
TESTOSTERONE 50 MG. PER DAY
TESTOSTERONE 50 MG. PER DAY
NITROGEN BALANCE
3-DAY PERIODS

The Effect of Cortisone Acetate Alone and in Combination with Testosterone Upon the Nitrogen Balance of a Man with Chronic Lymphatic Leukemia.

This metabolic balance evaluation on a 56 year old man with chronic lymphatic leukemia (F.T., S.K.I. 95513) consists of two separate studies of 17 three-day periods each. The scales for the nitrogen balances in grams per 24 hours are given as the ordinate; the scale

of the 3-day periods is given as the abscissa. The balances are charted as deviations from the average of the control periods rather than as the balances actually measured. N. = nitrogen. All the steroids employed were prepared as microcrystalline, aqueous suspensions and administered intramuscularly in four divided doses daily at six-hour intervals.

It will be seen that cortisone acetate alone caused a markedly negative nitrogen balance that gradually diminished to nitrogen equilibrium as the therapy was continued, and then became negative again when the dosage was increased. When testosterone was administered simultaneously with cortisone acetate, there was a moderate negative nitrogen balance during the first 8 days of therapy, and thereafter a moderate positive nitrogen balance which persisted as the therapy was continued and which was maintained even when the dosage of cortisone acetate was doubled. This is evidence that the adverse effects of corticoid therapy on protein tissues can be reduced or prevented by the simultaneous administration of an anabolic steroid.

(For further discussion, see text. Data recharted from *Figures 8 and 9* in Pearson and Eliel,[3] and reproduced with the permission of the authors and Recent Progress in Hormone Research.)

FIG. 14

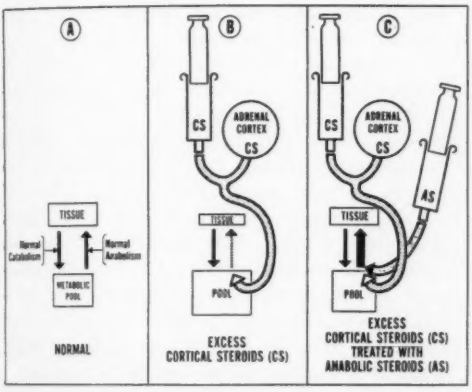
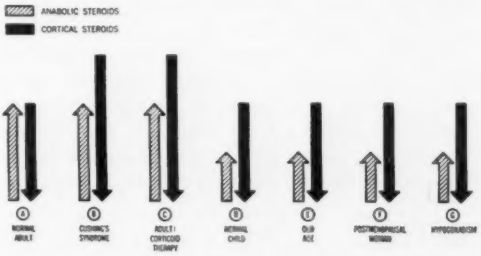


Diagram Illustrating the Mechanism by which Excess Cortical Steroids of Endogenous or Exogenous Origin Induce a Decreased Total Mass of Protein and Osseous Tissues, and the Mechanism by which Treatment with Anabolic Steroids Reduces or Prevents These Adverse Effects.

The rectangles represent the tissues (protein or osseous) and the metabolic pool; the size of the rectangles represents the total quantity of the mass of protein or osseous tissues and the total quantity of material in the metabolic pool; the arrows represent the metabolic processes, anabolism and catabolism; and the size of the arrows represent the rates of these metabolic processes. C.S. = cortical steroids; A.S. = anabolic steroids. The syringe with C.S. = cortical steroids of exogenous origin; the circle labeled adrenal cortex and C.S. = cortical steroids of endogenous origin; the syringe with A.S. = anabolic steroids of exogenous origin.

The diagram has three divisions: A—the normal total mass of protein or osseous tissues that results from the dynamic equilibrium between these tissues and the metabolic pool when the rates of anabolism and catabolism are both normal; B—the decreased total mass of protein or osseous tissues that results when the rate of anabolism is decreased by the anti-anabolic effect of excess cortical steroids of endogenous or exogenous origin (in this division the rate of catabolism is normal); and C—the partially restored total mass of protein or osseous tissues that results when the anti-anabolic effect of the excess cortical hormones on the rate of anabolism is partially offset by the stimulating effect of anabolic steroids of exogenous origin on the rate of anabolism (in this division the rate of catabolism is normal). It will be seen that this diagram illustrates the rationale for the use of anabolic steroids in controlling the adverse effects of corticoid hormones on protein and osseous tissues. (For further discussion, see text.)

FIG. 15



Schematic Diagrams to Illustrate the Relative Effect of Anabolic Steroids and Anti-anabolic (Cortical) Steroids upon Protein and Osseous Tissue Anabolism in Various Physiologic and Pathologic States.

An arrow pointing upward represents a stimulating effect; an arrow pointing downward represents an inhibiting effect; the length of an arrow indicates the amount of effect. The hatched arrows = anabolic steroids; the black arrows = cortical steroids.

The relation between the endogenous levels of anabolic and anti-anabolic steroids is shown for seven states: A—the normal adult, B—Cushing's syndrome, C—the normal adult receiving chronic corticoid therapy, D—the normal child, E—old age, F—the postmenopausal woman, and G—hypogonadism with normal adrenal cortical function.

It will be seen that there is a balance between the hormonal influences in the normal adult (diagram A), that there is an absolute increase in the anti-anabolic action in Cushing's syndrome and in the normal adult receiving chronic corticoid therapy (diagrams B and C), and that there is a relative increase in the anti-anabolic action (as a result of a decrease in the anabolic action) in the normal child, in old age, in the postmenopausal woman, and in hypogonadism with normal adrenal corticoid function (diagrams D, E, F, and G). (For further discussion, see text.)

Discussion

1. *The Action of Corticoid Hormones*

The author's concept of the action of corticoid hormones is as follows: (1) One of the primary actions of these substances is to increase the amount of available carbohydrate;

this necessitates an increase in the rate of conversion of amino acids and/or fatty acids into carbohydrate. (2) The increased rate of conversion of amino acids and/or fatty acids creates a demand for an increased supply of amino acids and/or fatty acids. (3) The demand for amino acids and/or fatty acids is offset first by amino acids and/or fatty acids from the diet. (4) If the demand is not satisfied by the carbohydrate precursors (amino acids and/or fatty acids) that are available from the diet, amino acids and/or fatty acids are diverted from the anabolism of protein and/or fat tissues. (5) If the demand still is not satisfied by the precursors from the diet and by those from the decrease in tissue anabolism, amino acids and/or fatty acids are supplied by an increase in the breakdown of protein and/or fat tissues. (6) The interpretation of the changes in the metabolic processes involving fat tissue is complicated by the fact that a portion of the excess newly-formed carbohydrate is reconverted into fat.

Three corollaries of this concept should be emphasized: (1) The amount of corticoid hormones determines the intensity of the demand for amino acids and/or fatty acids. (2) The total quantity of carbohydrate precursors in the diet in relation to the amount of corticoid hormones determines whether the demand for amino acids and/or fatty acids results in: a) no effect, b) an anti-anabolic effect, or c) an anti-anabolic and a catabolic effect upon the protein and/or fat tissues.[178-180] (3) When the total quantity of precursors is deficient in the intake, the composition of the diet determines whether the alteration in tissue metabolism as a result of corticoid hormones affects primarily the protein tissues or the fat tissues.[139-141,177,181] In other words, a high intake of fat tends to have a sparing effect upon protein tissues and vice versa, while a high intake of protein tends to have a sparing effect upon fat tissues and vice versa. This concept of the action of corticoid hormones is consistent with the observations that have been cited, and provides an explanation for the adverse effects of these substances on protein and osseous tissues.

2. *Anabolic Versus Gonadal Actions of Steroids*

Anabolic steroids have favorable effects upon protein and osseous tissues characterized by an acceleration in protein deposition and an increase in bone anabolism. Since qualitatively identical effects are induced by both androgen and estrogen, the somatotropic or anabolic properties of these hormones presumably are independent of the masculinizing or feminizing actions of these substances. Thus far, no anabolic steroid has been found which lacks these gonadal hormone actions; it is hoped that one will be discovered. It is clear, however, that the term "androgenic" cannot be employed as a synonym for "anabolic;" all of the known androgenic compounds are anabolic, but not all of the anabolic substances are androgenic (for example, estrogen is anabolic but not androgenic).

3. *The Recognition of Tissue Depletion*

There are no precise methods by which the initial and early states of protein depletion readily can be recognized. Similarly, osteoporosis escapes recognition as a clinical entity until it is sufficiently advanced to cause symptoms, spontaneous pathologic fractures, or an unquestionable increase in radiolucency, at which time it has been estimated that the total bone mass has been reduced by 30 to 50 per cent.[182,183] It is obvious, however, that the mechanism by which these adverse effects are induced begins to operate as soon as the endogenous levels of cortical hormones become elevated. Measures to prevent these unfavorable manifestations of corticoid therapy, therefore, must be instituted before protein depletion and osteoporosis can be recognized as clinical entities, and preferably as soon as chronic therapy with corticoid hormone preparations is initiated.

4. *The Recognition of Tissue Repletion*

Attention has been called to the difficulty in recognizing the initial and early states of protein depletion and osteoporosis. The same difficulty exists in evaluating the early stages of protein tissue repletion and osseous tissue regeneration. It seems probable that an unquestioned increase in radio-opacity of an osteoporotic bone cannot be established until nearly all of the missing bone mass has been restored; based on the rate of calcium storage in metabolic balance studies of patients with Cushing's syndrome, this will take at least 4 to 8 years! It is not surprising, therefore, that roentgenograms are of no assistance in evaluating the initial effects of

anabolic steroids on osteoporosis. Unfortunately, many of the trials of anabolic steroids in patients with excess corticoid hormones have been terminated after inadequate intervals because of lack of evidence in roentgenograms. These short-term studies provide no proof that anabolic steroids are failing to have a beneficial effect upon the protein and osseous tissues of patients with excess corticoid hormone levels, and in view of the other data which have been cited, conclusions based on such studies must be disregarded.

Conclusions

1. Cortical materials have adverse effects upon the protein and osseous tissues, characterized by protein depletion and osteoporosis.

2. These unfavorable effects result in most instances from an anti-anabolic effect of the corticoid substances upon the protein and osseous tissues.

3. The protein depletion and osteoporosis of Cushing's syndrome results from an absolute excess of endogenous cortical hormones.

4. The protein depletion and osteoporosis of old age, the postmenopausal state, and hypogonadism with normal adrenal cortical function may result in part from a relative excess of endogenous cortical hormones.

5. The protein depletion and osteoporosis of patients on chronic corticoid therapy results from an excess of administered corticoid hormones.

6. The susceptibility to protein depletion and osteoporosis during chronic corticoid therapy is increased: a) in patients who tend to have a relative excess of endogenous cortical hormones, such as children, elderly persons, postmenopausal women, and patients with hypogonadism and normal adrenal cortical function; b) in patients who have hypogonadism combined with adrenal cortical deficiency so that they lack sufficient endogenous anabolic steroids to offset normal replacement amounts of corticoid medication; and c) in patients who have malnutrition, inadequate intake of protein and/or minerals during corticoid therapy, disturbed function of the gastrointestinal tract with poor absorption of protein and/or minerals, pre-existing osteoporosis or other chronic systemic bone disease, marked restriction of physical activity or enforced bed rest during the corticoid therapy, chronic acidosis or other general or renal disorders with hypercalcuria, and similar conditions.

7. The susceptibility to protein depletion and osteoporosis during chronic corticoid therapy is decreased in patients who tend to have a relative or an absolute excess of endogenous anabolic hormones, such as patients with anabolic hormone-producing tumors of the gonads, individuals with the adrenogenital syndrome, and patients with acromegaly or gigantism.

8. Corticoid steroid therapy in adequate amounts is indicated to offset the effects of excessive amounts of endogenous anabolic hormones upon protein and osseous tissues in patients with hormone-producing tumors of the gonads, with the adrenogenital syndrome, or with acromegaly or gigantism.

9. Gonadal hormones (androgen and/or estrogen) have favorable effects on the protein and osseous tissues, characterized by increased growth of protein structures and of bone.

10. These beneficial effects result from an anabolic effect of the androgenic and/or estrogenic agents upon the protein and osseous tissues.

11. Anabolic steroids stimulate protein and osseous tissue anabolism: a) even when excessive corticoid activity is present, and b) without interfering with the beneficial corticoid actions.

12. Anabolic steroids counteract and control the adverse effects of corticoid hormones upon the protein and osseous tissues.

13. The favorable effect of anabolic gonadal steroids administered simultaneously with corticoid substances results from the anabolic action of the gonadal agents offsetting the anti-anabolic action of the corticoid agents upon the protein and osseous tissues.

14. Anabolic steroid therapy in adequate amounts for sufficient time is indicated *to restore* the protein and osseous tissues in patients who have protein depletion and/or osteoporosis associated with Cushing's syndrome from benign lesions, with old age, with the postmenopausal state, with hypogonadism and normal adrenal cortical function, and with prolonged and/or intensive corticoid therapy.

15. Anabolic steroid therapy in adequate amounts for sufficient time is indicated *to prevent* adverse effects upon protein and os-

seous tissues: a) in patients who are being started on a regimen of chronic corticoid medication; and b) in persons who are becoming elderly, in women at and after the menopause, and in patients with hypogonadism and normal adrenal cortical function.

16. In patients who are receiving chronic corticoid therapy, the anabolic steroid dosage should be maintained at an amount which is sufficient to prevent hypercalcuria (which indicates an adverse corticoid hormone effect upon bone).

17. The combination of androgen with estrogen appears to be the most potent and the most practical anabolic preparation now available for either the treatment or the prevention of the adverse effects of corticoid hormones upon the protein and osseous tissues.

Summary

Corticoid materials [adrenocorticotropic hormone (ACTH), hydrocortisone (cortisol), cortisone, and related steroids] are employed extensively at the present time as beneficial therapeutic agents in a variety of disorders. These substances also *may have adverse effects upon the protein and osseous tissues,* characterized by protein depletion and osteoporosis. The unfavorable effects are believed to result from an anti-anabolic effect of corticoid hormones upon these tissues. *Gonadal hormones* (androgen and/or estrogen) *have anabolic effects upon the protein and osseous tissues.* These anabolic steroids stimulate protein and osseous tissue anabolism: a) even when excessive corticoid activity is present, and b) without interfering with the beneficial corticoid actions. Anabolic steroids are effective in countering and controlling the adverse actions of corticoid hormones upon protein structures and bones. Therefore, *anabolic steroids should be administered to protect and/or to restore the protein and osseous tissues in patients who are being given* prolonged and/or intensive *corticoid therapy,* or even moderate "physiologic" amounts of corticoids when endogenous anabolic hormone levels are low (as in panhypopituitarism, or in Addison's disease with hypogonadism), *and in patients who have* either an absolute *excess of endogenous cortical steroids* (as in Cushing's syndrome associated with benign lesions) or a relative excess of endogenous cortical steroids (as in old age, the postmenopausal state, or hypogonadism associated with normal adrenal cortical function).

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Discussion (Abstract)

Dr. Weldon J. Walker, San Antonio, Tex. I want to commend Dr. Reifenstein. I would like to raise a question,—that is, since atherosclerosis is a condition that is almost reaching epidemic proportions in the United States today, is it probably not wiser to confine our anabolic hormone to an estrogen which does not have a deleterious effect on the genesis of atherosclerosis and perhaps reserve the androgens which are known to have a deleterious effect on the process of atherosclerosis to the more severe, more acute, painful conditions since more people die from coronary atherosclerosis alone in this country than from all forms of cancer combined?

Dr. Reifenstein (Closing). Thank you, Dr. Walker, for your remarks. The question that has been asked is essentially this: "Does andogen have an atherogenic effect which contraindicates its use?" The answer is "No." Let me explain. It must be emphasized that the cholesterol-lipid-lipoprotein concept of atherogenesis, which has been the basis for extensive animal and human investigation, still is regarded by most experts in this field as a theory and not as an established mechanism for the pathogenesis of atherosclerosis. The evidence to date does suggest that under suitable circumstances androgenic and/or estrogenic steroids may induce alterations in the levels of certain of the lipid substances in the body fluids and in the tissues. It remains to be demonstrated, however, that alterations thus induced are primary factors in the causation, in the prevention, or in the elimination of atherosclerosis.

Furthermore, one of the leading investigators in this field, Dr. Jeremiah Stamler, in a recent review of this subject (Recent Progress in Hormone Research 11:449, 1955) surveyed data from man and from chicks, and concluded that significant coronary atherogenesis may proceed both in the presence and in the relative absence of androgen. On the basis of Dr. Stamler's conclusion, we believe that androgen is not a critical and/or an important factor in the development of atherosclerosis. On the other hand, we believe, as indicated in our paper, that androgen as an anabolic agent may be a critical and an important factor in the prevention and/or the control of the adverse effects upon protein and osseous tissues of chronic corticoid therapy.

Thus, the atherogenic potential of androgen appears to be so weak that it provides little or no justification for withholding the hormone therapy, especially when the steroid is strongly indicated for its anabolic properties.

In closing, I would like to express my appreciation to Dr. Sexton and Dr. Bird for honoring me with the privilege of being the Guest Lecturer of the Section on Medicine. I want to thank them also for the courtesies they have extended to me here at the meeting.

The Use of X-Ray Therapy in Inflammatory Conditions*

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The author reminds the reader that x-ray irradiation has been at times an effective aid in the management of certain inflammations.

Introduction

THE USE OF X-RAY in the treatment of inflammatory diseases has changed in the last decade due to the advent of the antibiotics. The x-ray is no longer the treatment of choice in such conditions as acute cellulitis, gas gangrene, carbuncle, erysipelas, mastoiditis, and others. Now, only on rare occasions is x-ray therapy of value as an adjunct in the management of such conditions. There is, however, a group of inflammatory diseases associated with glandular hypertrophy and cellular hyperplasia which can be effectively managed by x-ray treatment. It is this group of conditions which will form the major portion of this discussion.

Lymphoid cells, regardless of location, whether in tonsils, lymph nodes, interstitial follicles or bone marrow are most easily destroyed. Next in order of vulnerability are the polynuclear and eosinophiles of the blood. The extreme sensitivity of the lymphocyte and polynuclear cells to irradiation makes the treatment of such cells practical wherever located. Care, of course, must be exercised to protect the normal structures by shielding or avoiding irradiation wherever possible.

Hypertrophic Pharyngitis

A ring of lymphoid tissue in the upper pharynx surrounds the openings into the gastrointestinal and respiratory tracts. The lymphoid ring is composed of the lingual tonsils, palatine tonsils, the adenoid collections in the vicinity of the auditory tubes and the pharyngeal tonsils on the posterior wall of the pharynx. The pharyngeal tonsils complete the ring, but between the main masses of lymphoid tissue, smaller lymphoid follicles are interposed. Surgical removal of the palatine tonsils and adenoids (pharyngeal tonsils) is effective and advised. The remainder of the lymphoid masses are not very amenable to surgery, and can be better managed by irradiation when inflammed and hypertrophied. Acute upper respiratory infections have become both endemic and epidemic. It is probably the most prevalent disease affecting all the population. A bout of upper respiratory infection frequently results in a persistent hypertrophic pharyngitis. Although the condition is not serious, the patient seeks medical aid because of fullness in the throat, a frequent desire to swallow and excess mucus in the upper pharynx. In the more acute cases, low grade fever and some soreness on swallowing is noted. Deafness as a symptom is more often observed in children than in adults.

Irradiation, both ex-radiation and radium, have been effective in the management of hypertrophic pharyngitis. Although not as generally used; the x-ray is thought to be as effective as radium in the management of hypertrophic pharyngitis. It has the advantage of ease of application, especially in children, and also more of the involved area can be covered at one treatment.

In support of this contention, the following quotation is cited:

Queries and Minor Notes.[1]

"TO THE EDITOR: I would appreciate information on the use of radium (Crowe applicator) in the nasopharynx for the destruction of lymphoid tissue. Is there any definite evidence that carcinoma can result as a late radiation sequel? Is x-ray treatment to be preferred?

ANSWER: This form of therapy is still very popular and is producing the desired results in the usual percentage of cases. So far there is no definite evidence

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to show that carcinoma can result as a late radiation sequel. Some reports show patients followed for as long as 30 years without serious pathological consequences. Due to ease and simplicity of x-ray treatment in competent hands, this type of therapy has increased in popularity at the expense of the radium applicator."

In treating lymphoid tissue of the upper pharynx, many different ports of entry have been described in an effort to avoid the salivary and pituitary glands. A submaxillary port irradiates the submaxillary gland and also to a lesser degree the parotid and pituitary glands. An open mouth port, if large enough to cover the lymphoid ring, will also irradiate the parotid glands and most likely spray the pituitary. The lateral fields, when properly placed, will cover the upper pharynx, irradiate the duct and a major portion of the parotid gland. It is also extremely difficult to avoid the upper portion of the submaxillary gland. Despite the salivary irradiation, lateral fields are thought to be more practical and have been adopted as routine. The treatment factors for an adult are 200 r, 200 K.V., 50 cm. distance with a 0.5 mm. of copper and 1 mm. of aluminum filter added. The h.v.l. is 1.05 mm. of copper. A 10 cm. field is used. The anterior portion of the field, however, is masked with lead depending on the size of the patient's face, and also whether or not it is thought desirable to irradiate the turbinates. There are no vital structures in the anterior part of the face, and radiation of the edematous turbinates frequently gives the patient some relief from nasal stuffiness. At the end of five days, the patient is given a second treatment on the opposite side. At the end of a second five day period, the patient is given a third treatment consisting of a 150 r, the other factors being the same, to each side. This makes a total of 700 r through two lateral fields in a 10 day period. This dose is found adequate for symptomatic relief. The plan of treatment for children is modified in that the field is of variable size and only sufficient to cover the lymphoid ring. The first and second treatments are 150 r each. The third treatment is 100 r for each lateral port. The other factors are the same as those used in the adult. The total radiation in the 10 day period is 500 r. The eyes, thyroid and as much of the anterior face as possible are all well shielded.

Since the dose is small, nausea is exceedingly rare, and the patient is not warned of such a possibility. Swelling of the parotid gland in from 4 to 8 hours is a common complication. The patient is warned of such a possibility and advised to use an ice bag and an analgesic if the discomfort is too severe. The swelling usually subsides in from 18 to 24 hours. The same complication is frequently observed following the treatment of the other lateral port although it does not happen as frequently as after the first treatment. We do not recall any swelling of the salivary glands on either side after the third treatment. Shortly after the series of treatments is completed, a few patients complain of dryness of the mouth and a disturbance in taste. The dryness results from decreased secretion of the salivary glands. The disturbance in taste is either secondary to the decreased salivation and/or a disturbance in the taste buds themselves as a result of the radiation. Neither symptom persists more than a few days. Relief is usually obtained by chewing gum or its equivalent.

Accurate evaluation in such cases is difficult. When a patient becomes symptom free of a condition of this magnitude, he rarely returns for observation. A 5 year segment of 375 patients treated was reviewed, and it was found that 5 per cent of the patients returned for additional treatment in the same year, 10 per cent returned for treatment in other years, and none had more than three series of treatments. Twelve per cent of those treated were children. Four per cent started treatment but did not finish the series for various reasons. The 15 per cent who returned for further treatment had had symptomatic relief, but a recurrence had followed additional bouts of acute infection. The 4 per cent who did not finish the series are of little importance in evaluating results, but from daily contacts with patients receiving x-ray therapy for benign conditions, I believe that a large percentage of these were either frightened by the word x-ray or imagined themselves to have a cancer about which they had not been informed. The press has so thoroughly fixed in the minds of the public the association of radiation and cancer that it is frequently difficult to treat a patient for a benign condition. Patience and diplomacy is frequently required on the part of the referring doctor as

well as the radiologist. Better education of the patient on the use of irradiation in benign conditions would be of value. With the best information available, it is the opinion in our office that from 70 to 80 per cent symptomatic relief is obtained in x-ray treatment of hypertrophic pharyngitis. Other writers report from 60 to 90 per cent symptomatic relief. In no case was there any permanent dryness of the mouth or permanent disturbance of taste. Sufficient time has elapsed for many of the children treated to mature. No growth disturbances of bones of the face or delay in tooth development has been observed. No legal complications have arisen.

Thyroiditis

Subacute thyroiditis, accompanied by cervical pain radiating upward sometimes as far as the ears, dysphagia, low grade fever, induration of the thyroid, and other symptoms, is very effectively managed with x-ray radiation. The usual routine of treatment is 150 r at 200 K.V. with 50 cm. distance, 0.5 mm. of copper and 1 mm. of aluminum filter with a field of sufficient size to cover the lateral thyroid area. The patient is given a treatment every other day on alternate sides for four treatments making a total of 600 r in a period of eight days. The results as a rule are very gratifying. The patient is usually comfortable by the time the series is completed and all symptoms of the disease have disappeared in from 15 to 20 days. Surgery will cure subacute thyroiditis, but x-ray therapy is so simple and effective that surgery is not necessary. X-ray in this dosage is not harmful and no remote complications have been reported.

Parotitis

Parotitis, both acute and chronic, responds well to radiation therapy. Acute parotitis usually occurs as a postoperative complication of serious operations. X-ray treatment is a method of choice. The treatment consists of daily doses of 150 r with either 0.25 or 0.5 mm. of copper filter and 1 mm. of aluminum. The field should be of sufficient size to amply cover the gland. Either 140 K.V. or 200 K.V. can be used. If the patient's condition is serious, 75 r twice daily is recommended. X-ray therapy is not always effective and sometimes the inflammation goes on to suppuration. A type of chronic parotitis with recurring acute episodes is seen in children, and is frequently mistaken for mumps until the patient has suffered many recurring attacks. A sialogram of the parotid gland usually proves the diagnosis. These cases respond well to 150 r given over the parotid area at three to five day intervals for three treatments. A voltage range of 140 K.V. to 200 K.V. with appropriate filtration is used. If symptoms return another series can safely be given. Since these cases all occur in children, care should be taken to protect other structures that might be damaged by radiation.

Folliculitis and Suppurating Hidradenitis

Folliculitis and suppurating hidradenitis is characterized by multiple furunculi in the axillas, groins, breasts, perianal region, bearded area of the face and the back of the neck in men. The condition is thought to be due to external causes such as irritation from depilatories, shaving, friction from tight clothing and excessive sweating. X-ray treatment for infection of the hair follicles and sweat glands is effective provided sufficient irradiation is given to produce epilation and reduce the secretions of the sweat glands. Either of two methods can be used. (1) An epilation dose to the hairy areas can be given at the initial treatment, allowing sufficient time to lapse until epilation is complete; the infection will usually subside. (2) Fractionated doses may be used two to three times weekly until there has been sufficient saturation to produce epilation and some diminution in the secretions of the sweat glands. The latter method probably is more effective, especially in treating the axillas where there is more pain, induration and chronicity than in other locations. Since the infection arises from the appendages of the skin and is relatively superficial, a kilovoltage range from 90 to 200 with appropriate filtration can be used. There is less risk of permanent skin damage with the high voltage and heavy filtration.

Pancreatitis

Heacock and Cara[2] reported 53 cases of acute pancreatitis in which they had used x-ray treatment. The following factors were used—2 mm. of copper, h.v.l. 200 K.V. through a 15 by 15 cm. port; the skin target

distance was 50 cm. The usual dose was 200 r daily for three days making a total of 600 r. More than one series of treatment was necessary in 12 of the 53 cases. Their results were good in 62 per cent, fair in 29 per cent, and poor in 9 per cent. They concluded that regardless of etiology, deep x-ray therapy is to be advocated in conjunction with supportive measures for all cases of pancreatitis.

Bursitis

Bursitis as a whole is too extensive a subject for this discussion, but several cases of bursitis of the hand occurring in patients whose business required an excessive amount of hand shaking have recently been seen. The term, "Hand Shakers Disease," has been coined to apply to such cases. The lesions are red, swollen, painful and periarticular in location. Calcifications can be demonstrated on the radiograph. X-ray therapy is most effective. The routine treatment is 150 to 200 r, 200 K.V., 0.5 mm. copper, 1 mm. of aluminum filtration at a 50 cm. distance. A field of sufficient size to amply cover the involved area is used. The treatments are given at three to five day intervals for a total of three. The symptoms have usually subsided by the time the last treatment is given. If symptoms persist beyond the third treatment, additional doses may be given.

Nonspecific and Tuberculous Adenitis

X-ray is still of value in the treatment of nonspecific adenitis, especially where drug therapy has failed. It can also be used as an adjunct to surgical treatment. In treating a firm acutely inflamed gland, a daily dose of 100 to 125 r is given over the involved area with 3 mm. of aluminum or 0.25 mm. of copper as filter at 140 K. V. In glands that show subacute or chronic inflammation, the same dose is given every other day. From three to six treatments are usually sufficient to produce marked resolution. If no improvement is noted by the sixth treatment, it is advisable to discontinue x-ray therapy.

Tuberculous adenitis can be successfully managed by the proper use of x-ray therapy. It is desirable that treatments be given before the node becomes necrotic. This, however, is not always possible, and even though the node is necrotic, healing can be accelerated by the use of radiation. The residual inflammatory exudate is absorbed more rapidly, and the drainage period is shortened. The hard node in a large percentage of the cases regresses without either drainage or scarring. The plan of therapy is one treatment of 125 r every 5 to 7 days using 3 mm. of aluminum or 0.25 mm. of copper at 140 K. V. An ample field to cover the involved area is used. From four to six treatments are given. The series can be repeated in from four to six weeks if resolution of the nodes is not complete.

Summary

1. X-ray irradiation is a safe, easy, effective method of controlling hypertrophic lymphoid tissue of the upper pharynx in both children and adults. No remote complications or sequelae have been observed.

2. Subacute thyroiditis is easily managed by x-ray therapy. The clinical symptoms disappear rapidly, and no serious complications have been reported.

3. X-ray therapy is a treatment of choice in both acute and recurring parotitis. The results are good.

4. Folliculitis and hidradenitis are controlled by the use of sufficient radiation to remove the hair and depress the secretion of the sweat glands.

5. The use of x-ray therapy is advised in acute pancreatitis in conjunction with supportive measures.

6. Bursitis of the hand responds as well as, if not better, to x-ray therapy than does bursitis of ther parts of the body.

7. X-ray therapy is still of value in connection with drug therapy in the management of both nonspecific and tuberculous adenitis.

References

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Discussion (Abstract)

Dr. Vincent Collins, Houston, Tex. I hope that "pinch-hitting" for Dr. Eskridge will permit me to do justice to this very excellent review of the indications and technics for the use of radiation in the inflammatory and infectious group of diseases. This is something that even radiologists have tended to neglect, and many of our better clinicians have forgotten there was ever a place for it.

To suggest to our modern surgical residents that radiation may be useful in acute pancreatitis is received with the same amazement as an order for a turpentine stupe. An exploratory laparotomy, opening of the duodenum and a sphincterotomy is considered a more reasonable approach.

There are three factors that account for the lack of interest and enthusiasm for the use of irradiation in this group of diseases. The first is just lack of knowledge of the effects of radiation. These have largely been forgotten since the advent of anti-inflammatory and anti-infectious agents.

Dr. Seibold of Wichita Falls has called my attention to a recent article, which reports 200 deaths in the past year due to the use of antibiotics. Antibiotics are not an innocuous approach to the treatment of infectious lesions, and all too often they are ineffective in the treatment of inflammatory lesions because the two are apt to be confused.

The increase in sensitization of patients and desensitization of bacteria is of some concern in the appraisal of the present place of antibiotics. There is something left for radiation to do where its effects have been demonstrated in the fields that have been discussed for you by Dr. Gray.

The third reason, of course, is the threat of carcinogenesis that is always with us. There are recent articles, one by Simpson, Hempelmann and Fuller in the *Journal of Pediatrics,* and one by Clark in a recent issue of the *J.A.M.A.* which deal with the incidence of carcinoma of the thyroid in children who had radiation of the thymus in infancy. This is a very serious matter but the evidence must be scrutinized closely for several reasons. Yesterday, Dr. Cargill pointed out to us that despite the fear that radioiodine might be carcinogenic, there has been no known instance of cancer occurring among the patients who have been treated by this method over the past 15 years.

As another example, thousands of youngsters have had depilation of the scalp by x-ray. I have encountered no incident or report of cancer developing in the treated area. Thousands of patients in the adult group have been treated for carcinoma of the cervix. There have been fractured hips and other radiation sequelae. but I have not encountered leukemia, lymphoma, carcinoma or sarcoma in the irradiated area in the surviving patients.

There is still an important place for the use of irradiation in the treatment of inflammations and infections. The risk of antibiotics appears to be more real than the hazards of radiation.

Dr. Martin Schneider, Galveston, Tex. The importance of radiation therapy in inflammatory diseases is a subject that should be discussed over and over again, as the essayist has today, because of the tremendous advantage of this method in all types of inflammations, regardless of etiology. The very nonspecificity of action of ionizing radiation in inflammatory processes is actually an advantage in many cases, in which the etiologic agent is either not identified or proves resistant to presently known antibiotics or chemotherapeutic agents. This nonspecificity of action depends upon its activity on the cellular reactive bed of a focus of inflammation, rather than on the bacteria, fungi or other agents themselves, according to the best available evidence. We may even wonder whether radiation therapy for inflammation may not assume more importance in the light of evidence which was demonstrated by Dr. Dean Dukes that, among some 96 strains of staphylococci studied over a period of about ten years, resistance to penicillin increased considerably even during the first few years, and to a lesser extent, the same trend may have begun for the other antibiotics although the evidence for the latter had not yet been studied long enough to be conclusive, at the time Dr. Dukes and I discussed it.

Dr. Peter E. Russo, Oklahoma City, Okla. I enjoyed Dr. Gray's paper very much. The percentage of patients that I treat for benign disease has dropped considerably in the last seven or eight years. However, I have a little ray of hope lately, because some of the surgeons have referred patients to me before operation for pilonidal cyst. About three to four weeks prior to operation, especially in those who have dense hair in the area, for an epilation dose of radiation, it helps in keeping the dressings clean; the patient has less trouble changing the bandages and things of that sort. So I am getting a little work in these cases.

I also am receiving a few patients for the treatment of keloids about the face, neck, and thorax, especially in women. Just before I left, a patient returned to me whom I had treated several years ago for Marie-Strümpell arthritis, and he has carried on very well. This is the third series of treatments I have given him over the years, and with very good results. I thought it would be worthy of mention that we still treat Marie-Strümpell arthritis.

Dr. Gray (Closing). I would like to thank all the gentlemen for the kind discussion, and would like to thank Dr. Collins, particularly, for being so kind in his remarks.

I am sorry we had to include only those conditions that ended in "-itis." I would like to have included keloids and some of the other benign conditions, but time would not permit.

Compression Neuropathy of the Median Nerve*

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The diagnosis of compression neuropathy of the median nerve is not infrequently missed and is usually made only after motor signs or muscular atrophy appear. For relief of pain and complete restoration of function early diagnosis is essential.

COMPRESSION OF THE MEDIAN NERVE may occur at any point along its course. The most frequent sites of compression of this nerve are in the wrist, hand, upper volar surface of the forearm, and supracondylar region of the elbow (Fig. 1). Of 345 cases with lesions of the median, ulnar or radial nerves resulting from all causes seen and recorded at Duke Hospital as of January 1955, there were 27 patients and 34 instances of compression neuropathy of the median nerve. None of the patients selected for inclusion in this group had an associated history of laceration, fracture, dislocation or severe contusion. Fourteen of the patients had compression of the median nerve occurring in the carpal tunnel at the wrist, two showed compression in the hand, ten in the pronator region of the forearm and one just above the elbow.

Pathology

The pathologic changes which take place in the compression neuropathy under discussion are usually of the "first degree."[1,2] In this degree, there is no actual loss of continuity or degeneration of nerve fibers other than localized vacuolization of the myelin. Local edema and cellular infiltration may also be present.[3]

Proprioceptive and motor functions are more vulnerable in "first degree" injury than are the functions of pain, touch and sympathetic activity. The mechanism of the loss of these properties in compression neuropathy is not clearly understood, but it is thought to be due to ischemia and/or axonal injury as the result of external pressure.

These "first degree" nerve changes are readily reversible. If the mechanism causing these alterations is unrelieved, "second degree" nerve damage may occur. The axonal injury will then progress, leading to Wallerian degeneration distally as well as changes for a short distance proximally.[3]

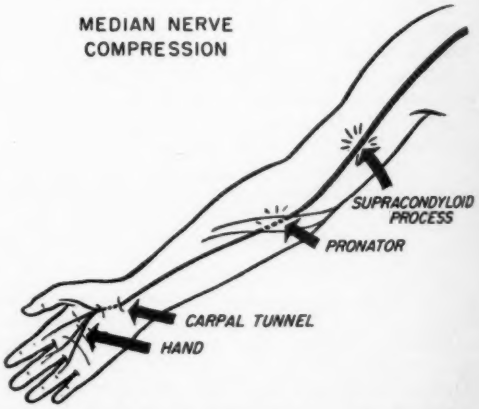
Thus, with prolonged, moderate nerve compression, one may expect slow recovery and, in some instances, incomplete recovery even after relief of the compression.

Compression of the Median Nerve in the Hand

There were two patients with compression of the median nerve in the hand in this series.

Case 1. A 45 year old dentist gave a history of several years of progressive weakness of the thumb and index finger and atrophy of the thenar eminence. No sensory change had occurred. Direct pressure in

FIG. 1



The common points of compression of the median nerve in the hand, wrist, forearm and supracondylar area.

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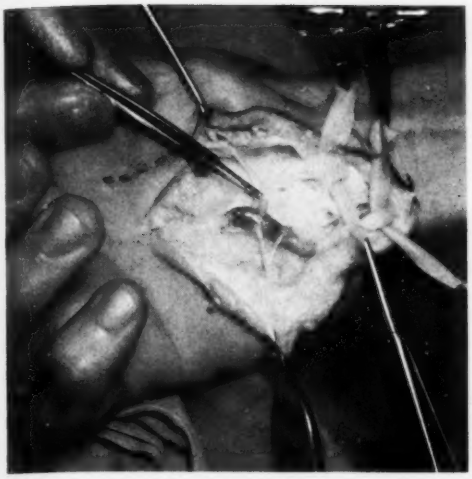
FIG. 2



Long standing thrombosis of the ulnar artery. The motor branch of the median nerve is opposite the artery. When the hand was cupped and squeezed the firm thrombus compressed the small motor branch of the nerve and resulted in paralysis of the intrinsic muscles of the thumb. No sensory deficit was present.

the palm just to the radial side of the hypothenar muscles, in line with the ring finger, caused pain. There was no pain over the course of the median nerve. Two centimeters distal to the carpal crease, a pea-sized tender mass was palpable. Prior to examination the patient had not been aware of this finding. Exploration of the hand revealed a lobular, thrombosed aneurysm of the ulnar artery which had been causing intermittent compression of the recurrent motor branch of the median nerve (Fig. 2).

Case 2. A 43 year old man, crutch walker, complained of numbness, hypesthesia and tingling in the thumb, index, long and ring fingers of six weeks duration. There was callous formation at the base of his palm. Weakness of opposition was present. These findings were interpreted as being due to direct pressure over the median nerve in the hand. The patient did not return to the clinic for follow-up.

With relief of local external pressure, complete recovery usually occurs.

Compression of the Median Nerve at the Wrist (Carpal Tunnel Syndrome)

Compression of the median nerve in the carpal tunnel, frequently recognized in recent years, was described in 1913 by Marie and Foix.[4] They found, at the autopsy of a patient with bilateral thenar atrophy, bilateral median nerve "neuromata" just proximal to the transverse carpal ligament. The authors suggested that section of this ligament might give relief in patients with symptoms arising from median nerve compression.

In 1945, Zachary[5] reported two cases of compression of the median nerve at the wrist. In both of these, old bone deformity was present and, at operation, the surgeon demonstrated compression of the median nerve by the carpal ligament.

Cannon and Love,[6] in 1946, reported 38 cases of "Tardy Median Palsy." In nine of these, operation was done and satisfactory results reported. In three of the nine patients no definite etiology could be established.

The association of compression of the median nerve at the wrist with acromegaly has been noted. Woltman,[7] in 1941, presented two such cases. In one of his patients, the skin was anesthetic to the extent that ulcers developed on the finger tips.

This syndrome of nerve compression occurs more frequently in women than in men and is usually noticed between the ages of 35 and 55. Phalen,[8] in 1951, indicated that 10 of his 11 patients were women. He considered the similarity between carpal tunnel syndrome, DeQuervain's disease and "trigger finger," since all show reactive fibrosis and require similar treatment. One of his patients did have associated DeQuervain's disease and another had a "trigger finger." The predominance of women in Phalen's series is substantiated by other authors.

Etiology. (Table 1). (1) Bone Deformity. The neuropathy may be associated with osteoarthritic changes in the wrist joint or it may occur following fractures of the wrist bones. The compression syndrome, which may occur several years after the appearance of a known bone deformity is sometimes called "Tardy Median Palsy." (2) "Spontaneous." In many instances, the median nerve palsy arises without a history of any known injury and without definite anatomic deformity.

The pathogenesis of this nerve lesion has been the subject of much speculation. It has been stated that the lesion is in the motor branch to the thenar muscles as it passes over

TABLE 1

ETIOLOGY OF MEDIAN NERVE COMPRESSION

1.	No specific known cause
2.	Repeated minor trauma
3.	Thickening of synovial tissue, flexor tendons
4.	Result of old recognized trauma
5.	Ganglion or other mass in carpal tunnel

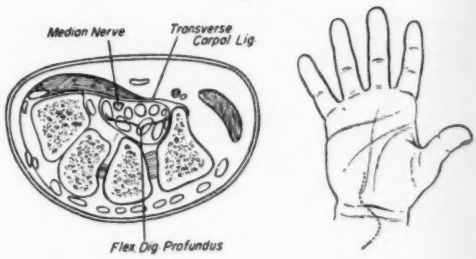
the distal edge of the carpal ligament. Other observers[9] have stated that, because of their late development in man, the thenar muscles are especially susceptible to injury and degeneration. Neither of these observations account for the sensory change which is frequently the outstanding symptom. During the past several years, compression of the median nerve within the carpal canal has been emphasized, and the syndrome has been more frequently diagnosed.

In certain patients with "spontaneous" compression, specific etiologic factors have been found contributing to this localized compression of the nerve beneath the carpal ligament. Rheumatoid arthritis associated with thickening of the synovial sheaths of the flexor tendons was demonstrated in one patient (Fig. 3); while in another, nerve compression was due to a ganglion within the carpal canal. Also, the presence of excessive fat within a small carpal tunnel or within the sheaths of the flexor tendons, such as is seen in a patient with a rapid gain of weight, could be a contributing factor. The presence of this fat or connective tissue and the fact that the carpal canal in women is usually smaller than in men, might help to explain the predilection for compression in women. Repeated unrecognized minor trauma with associated tenosynovitis of the flexor tendons may be a causative factor in some patients. In this series, 7 of the 14 cases were bilateral, which suggests the occurrence of this syndrome in persons having a general tendency to reactive fibrosis.

FIG. 3

Wrist area in rheumatoid arthritis in a patient who noted diminished sensation over the median nerve distribution, bilaterally. The other wrist was similar, the tendon sheaths were hypertrophied and the small carpal canal contained an excessive amount of soft tissue. The nerve was compressed by the transverse carpal ligament. At operation the synovial sheaths were removed after the carpal ligament was incised. Symptoms subsided rapidly. Incision of the ligament without excision of tendon sheaths is not sufficient if the sheaths are hypertrophied.

FIG. 4



1. Rough anatomic relationship of the median nerve to the profundus and sublimis tendons, the carpal bones and the transverse carpal ligament. 2. Curved incision is preferable to the transverse incision, so that the entire carpal canal can be explored and, if necessary, the hand entered.

Anatomy. In the carpal tunnel, the median nerve is confined by structures that do not readily yield to increased internal pressure. As the nerve passes from the forearm into the hand, it lies just beneath the firm transverse carpal ligament and is surrounded on the dorsum and laterally by the carpal bones and the flexor tendons (Fig. 4). In this closed space, the nerve is vulnerable to compression. After passing beneath the carpal ligament, the median nerve gives off the recurrent motor branch to the thumb which supplies the opponens, abductor brevis and the superficial head of the flexor brevis. The main nerve trunk sends sensory branches to the thumb, index, long, and radial half of the ring fingers.

Fourteen patients in this series had the carpal tunnel syndrome. Nine patients were women, 5 were men. The average age was 52 with the oldest being 69 and the youngest 34 years. This age distribution has a definite relationship to etiology.

Symptoms. The usual symptoms are numbness, tingling and burning pain along the median nerve distribution (Table 2). Frequently, only one or two fingers are involved instead of the thumb and the usual "two and one half" digits. In our group, symptoms occurred "spontaneously" in 10 of the patients. The remaining 4 cases are considered to be of spontaneous origin although trauma was men-

TABLE 2

SYMPTOMS OF MEDIAN NERVE COMPRESSION

1. Numbness
2. Tingling
3. Burning
4. Pain
5. Weakness
6. Hand fatigue

TABLE 4

SIGNS OF MEDIAN NERVE COMPRESSION

1. Hypesthesia
2. Atrophy
3. Painful mass at wrist
4. Positive Tinel's sign at wrist
5. Paresthesia with forced dorsiflexion (30 seconds) wrist
6. Paresthesia with forced volar flexion

tioned as a possible cause in each history. In Case 3, (Table 3), the symptoms occurred after the patient was hoeing in the garden. Symptoms started in Cases 5, 7, and 10 after the patients had been pruning bushes, doing woodwork and operating a hand printing press.

"Numbness" was a presenting complaint in 13 of the 14 patients listed in the table. Pain was present in 10 of the 14 patients. Five of the patients complained of either atrophy or weakness, and several complained of hand fatigue and a tendency to drop objects. Complete agreement is not present concerning the position of the wrist which causes the onset of symptoms in most patients. In studying the carpal canal structures, Abbott and Saunders[10] injected the median nerve sheath in cadavers with lipiodal and Berlin Blue and found that passage of the dye distalward was interrupted by acute flexion but not by extension of the wrist. Contradictory to these observations were the findings of Brain, Wright and Wilkinson[11] who, using manometric technic on patients, measured the amount of pressure required for the passage of fluid through a small tambour placed under the median nerve sheath beneath the transverse carpal ligament with the hand in different positions. They showed that pressure on the tube and, probably on the nerve, was greatest with the wrist in extension. Observations at Duke Hospital indicate that dorsiflexion is more likely to reproduce dysesthesia and paresthesia than volar flexion. Mechanically, this is verified by the fact that median nerve symptoms may occur immediately after a Colle's fracture with forced dorsiflexion, but flexion and ulnar deviation of the wrist when fixing the fracture does not usually produce median nerve compression.

TABLE 3

CASES OF CARPAL TUNNEL SYNDROME

Case	*Age*	*Affected Hand*	*Chief Complaint*	*Duration*	*Examination*	*Surgery*
1(CF)	54	Bilat.	Numbness Atrophy	2 yrs.	A,W,S	No
2(CF)	55	Right	Weakness	20 yrs.	W*,A	No
3(CF)	56	Right	Numbness	4 yrs.	A,S	No
4(WF)	49	Right	Numbness Pain	10 mos.	W,S	Yes
5(WM)	64	Bilat.	Numbness Pain Weakness	2 yrs.	W*,A	No
6(WF)	46	Bilat.	Pain	4 mos.	S,A	Yes
7(WM)	35	Right	Pain Numbness Pain	7 yrs.	A,W,S	Yes
8(WF)	41	Bilat.	Numbness	10 yrs.	Left-O Rt. A,W,S	No
9(CF)	34	Right	Numbness Pain	1 yr.	W,S	No
10(WM)	69	Left	Numbness Weakness	15 mos.	A,W,S	Yes
11(WF)	47	Right	Numbness Pain	1 mo.	W*,?A	Yes
12 (CM)	68	Bilat.	Numbness Pain	20 yrs.	A,W*,S	Yes
13(WF)	61	Bilat.	Numbness Pain	3 yrs.	A,W,S	Yes
14(WM)	57	Bilat.	Numbness Pain	5 mos.	S (dysesthesias)	Yes

A—Thenar atrophy
W—Weakness of abduction or opposition
W*—Weakness of both
S—Sensory changes—median

Signs (Table 4). (1) Sensory change was present in 11 of the 14 patients in our group. Hypesthesia to pin prick along the median nerve distribution below the level of the carpal ligament, with a varying degree of decrease in other sensory modalities, was the common sensory change. (2) Atrophy of the opponens muscle with weakness of opposition and/or abduction was present in 7 of the 14 patients (Fig. 5). (3) A palpable tender mass near the midline just proximal to the volar carpal ligament, indicated compression of the median nerve by this ligament. (4) A positive Tinel's sign just proximal to the volar carpal ligament is an added diagnostic aid. (5) Another good diagnostic test is the production of paresthesia in the fingers by forced dorsiflexion of the hand for 30 to 60 seconds. The paresthesia is relieved by dropping the hand to a neutral position. This test is usually positive when the nerve is swollen just proximal to the ligament. Occasionally, only volar flexion will produce symptoms.

FIG. 5

Comparison of thenar muscles in a hand in which there has been median nerve compression for about 12 months. A painful palpable mass was present in the wrist region in the hand wearing the watch band; the thenar muscles were atrophied; diminished sensation was present in the digits supplied by the median nerve. The patient was a waitress and the position of the wrist in carrying heavy trays is thought to have contributed to the compression of the nerve by the transverse carpal ligament. A tendon transfer for strengthening the thumb was done at the same time that the transverse ligament was incised, in order to restore function of the thumb rapidly. Sensation returned completely.

Diagnosis. If the onset of symptoms has been gradual and if no other definite cause has been established, the diagnosis may be confusing. The differential diagnosis includes neurilemmoma, cervical disc, syringomyelia, cord tumor, selective affectations of the brachial plexus, "scalenus anticus syndrome," peripheral neuritis, primary muscular atrophy, multiple sclerosis and Raynaud's disease.

Treatment. Cutting the transverse carpal ligament will relieve the symptoms and some of the signs of the "carpal tunnel syndrome." Prompt relief of numbness, tingling and pain, usually occurs following operation. A transverse incision allows satisfactory exposure of the nerve, but does not allow complete exploration of the carpal canal and, if necessary, the hand. The advantages of a curved, S-shaped, longitudinal incision are as follows (Fig. 4): (1) the ligament and nerve can be easily seen through the entire length of the carpal canal; (2) ganglion or enlargement of the tendon sheath can readily be seen; (3) the hand can be entered easily if there is a question of a lesion distal to the carpal ligament.

Recovery of motor power in the hand depends upon the duration and degree of compression of the median nerve. If the opponens muscle weakness and atrophy have been present for years, the likelihood of motor recovery is not good, and an opponens substitution tendon transfer may be done at the same operation in which the ligament is cut.

Compression of the Median Nerve in the Forearm

The median nerve may be compressed by the pronator teres muscle or by scar tissue resulting from trauma to the soft tissues of the forearm, other than the wrist.

The Pronator Syndrome. The median nerve, as it enters the forearm in front of the elbow, usually passes between the two heads of origin of the pronator radii teres. Dissection of 300 cadaver arms by Jamieson, Anson and Beaton[12,13] showed this relationship to be present in 83 per cent of the specimens. In the remainder variations did occur with the nerve passing through one of the heads or under both heads of the pronator muscle. In its proximal segment, the nerve crosses anterior to the ulnar artery, being separated from the artery only by the deep head of the pronator. As the nerve passes into the forearm, it is covered by the firm upper edge of the flexor digitorum sublimis near the point where the muscle inserts into the radius. The spread of the flexor sublimis from ulna to radius forms a small entry way for the median nerve into the forearm which may constrict the median nerve under certain conditions.[14] Compression of the median nerve in the upper portion of the forearm has been described by Seyffarth[15] and given the name of the "Pronator Syndrome." Seyffarth presented 17 cases of neuropathy which he ascribed to pressure from a firm tender pronator muscle. He described the most frequent symptoms as pain and paresthesias made worse by use of the arm, tenderness to pressure over the pronator muscle just above the median nerve, and hypesthesia over the median nerve sensory distribution. These patients were reported as showing improvement following one or two biweekly injections of Novocain into the tender pronator muscle. The extreme of this condition is a combination of constriction of the median nerve by the flexor sublimis and pronator teres plus ischemia as is seen in Volkmann's ischemic contracture secondary to trauma.[14] In the Duke series, there were 10 patients with a "pronator syndrome."

Case 1. (Pronator Syndrome) A 35 year old woman

had pain and swelling about the right forearm of four days duration with associated numbness of her thumb, index and long fingers. The symptoms were made worse by the extremes of pronation and supination. Palpation revealed tenderness in the region of the pronator teres muscle. Carrying the hand into full supination would cause subjective numbness in her hand. No sensory changes were noted on examination. The patient was treated with a plaster splint and aspirin and the symptoms subsided in about 10 days.

This was considered as a tenosynovitis with secondary pressure on the median nerve in a patient with a short fat forearm.

Case 2. A 40 year old white woman fell and struck her right elbow. Two or three days following the fall she developed progressive numbness of her index, long and ring fingers. Digital pressure over the pronator teres revealed tenderness and caused pain to radiate into the arm and hand. There was weakness of the short abductor muscle of the thumb. The patient was treated conservatively with gradual decrease in her symptoms.

The tender pronator muscle may have resulted from muscle hemorrhage or fascial tear and edema with subsequent nerve compression.

Case 3. A 59 year old white physician had numbness and weakness of his left thumb and index finger. Six months prior to admission he had noticed vesicle formation around the nail of the left thumb followed by similar lesions over the dorsolateral aspect of the forearm. Herpes zoster was considered. Four months before admission, he noted aching pains in his left forearm and numbness and weakness of the thumb and index finger. Physical examination revealed tenderness over the pronator teres and hypesthesia over the thumb and index fingers. Weakness of flexion of the thumb and index finger were noted. On exploration of the upper forearm, a fibrous band arising from the outer head of the pronator teres and flexor sublimis was found constricting the median nerve. The band was released[1] and the median nerve mobilized. Postoperatively, there was a decrease in the pain with improvement in sensation. Gradual improvement has occurred during the past year.

"Honeymoon Paralysis." Three patients with persistent symptoms of "honeymoon paralysis" were found in this series. The patients complained of awakening with numbness and tingling in the thumb, index, long and ring fingers following sleeping with the bed companion's head resting on the volar aspect of the patient's forearm. Usually, these symptoms subsided within a few hours, but in certain patients they persisted. Two of these patients had symptoms for several weeks with median sensory and motor changes. The third patient had symptoms for a few days consisting of subjective numbness of the index, long and ring fingers. Examination was negative. Recovery occurred spontaneously in all three.

Treatment of patients with compression of the median nerve as a result of the "pronator syndrome" and "honeymoon paralysis" is usually conservative. Reassurance is important.

Pronator and Forearm Muscle Contracture. The use of a supination cast in an effort to correct the contracture of the pronator teres and forearm muscles in cerebral palsy patients may result in pain and numbness along the median nerve distribution. Four patients have been seen with median nerve symptoms several hours after a long cast was applied to the forcibly supinated forearm. External compression of the median nerve by tight fascial bands and shortened muscles can account for nerve compression. Removal of the cast relieved the symptoms of compression within a few hours.

Compression of the Median Nerve Above the Elbow

Compression of the median nerve by the "supracondyloid process" of the humerus has been reported. Parkinson[16] described one patient and briefly reviewed the literature. This process is an exostosis arising from the medial aspect of the humerus about 5 centimeters proximal to the medial epicondyle. In many instances, this "spur" may go unnoticed, but in some patients, symptoms of median nerve compression occur. This pain and hypesthesia may be due to the passage of the nerve over the exostosis or through a foramen created by a fibrous band passing from the process downward to the medial epicondyle. This band may be an anomalous head of the pronator teres which, when it becomes tense or contracts, compresses the median nerve.

Relief of symptoms will occur after removal of the bone and the associated fibrous tract. In the Duke series, one patient had this syndrome. He was a 4 year old boy with intermittent pain and numbness in the thumb and index fingers of the right hand.[17] These symptoms usually came on when the patient was using the right hand for drawing. At operation, the nerve was seen to run over the exostosis. Excision of the bone resulted in complete relief.

Summary

Compression of the median nerve may occur at any point in its course. This review indicates that the four sites of predilection are the carpal tunnel, forearm, hand and just above the elbow. The syndrome is frequently labeled "spontaneous," but in this series a specific cause could be determined in over 50 per cent of the patients and a probable cause in about 25 per cent. The physician should keep this neuropathy in mind when seeing patients who have unexplained pain in the distribution of the median nerve. Prompt diagnosis and early therapy may prevent permanent crippling of the hand.

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Discussion (Abstract)

Dr. Frank F. Parrish, Houston, Tex. Drs. Bell and Goldner have brought us a very complete paper on a subject which is just coming to be recognized by orthopedic surgeons. They have had an unusual experience with a large number of cases. I, personally, have seen but three such patients, none of whom came to surgery. I think that in arriving at the diagnosis one must certainly be familiar with these conditions and have them in mind at the time of the examination. If conservative measures fail, then the response to operation is almost certain if it is not a neglected case.

50th Anniversary Meeting

Washington, D. C.

November 12-15, 1956

Milkers' Nodules*

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Charlottesville, Va.

This is an interesting condition met with in rural areas. It probably is more common than is thought because it may not be suspected as a disease entity.

MILKERS' NODULES IS A DISORDER of undetermined etiology which affects chiefly the skin of the exposed areas of persons who milk cows. It is possible that the disease was known to Jenner,[1] but it was first called to the attention of physicians under the name of milkers' nodules in 1899 by Winternitz.[2] The first report of the disease in the United States was made by Becker in 1940.[2] Milkers' nodules have been reported from England, Germany, France, South Africa, Finland, Jerusalem, Russia, and several areas in the United States, and it is likely that the disease occurs wherever cows are kept by man.[2-23]

Our interest in milkers' nodules was aroused by the observation of two patients with the disease in Virginia in 1952.[6*] Since that time we have encountered six more patients with the disorder.

Report of Cases

Case 1. E. M., a 42 year old white man, first noticed lesions on his right hand in March, 1952. When he was first seen in the Clinic (April 15, 1952) there were 11 lesions present on the right hand (6 on the thumb, 3 on the palm and one each on the third and fourth fingers). Most of the lesions were dome-shaped nodules with intact surfaces but two or three presented superficial erosion and crusting.

Cultures from intact lesions were negative for bacteria and fungi, the patient's white blood count was normal, and the Wassermann and Kline tests were negative.

The patient was given an antibiotic ointment to apply topically. He returned to the Clinic on April 26, 1952, because of lymphangitis of the right arm and lymphadenitis of the right axilla, which he thought followed a kick on the arm by a cow. The patient was admitted to the hospital where he was treated with penicillin by injection and wet dressings applied locally. There was prompt subsidence of the secondary infection. The entire course of the patient's illness was approximately three months.

At the time of onset of the disease the patient was milking cows with reddish nodules on the teats and udders. There were other people on the farm who milked the cows but they did not develop lesions. The patient had been a miner most of his life and he had only recently been milking cows. In addition, he had had a mild cerebrovascular accident which made the left hand unsuitable for milking.

Case 2. H. B., a 41 year old white woman, had been milking cows which had friable, easily bleeding nodules on the teats and udders. Early in May, 1952, a nodule appeared on the right palm and shortly thereafter lymphangitis developed in the right arm. The palmar nodule had been incised and the patient had been given penicillin before she was seen at the Dermatology Clinic on May 23, 1952. On May 23 there was a single granulomatous lesion about 1.5 cm. in diameter on the right palm. The patient was instructed to use magnesium sulfate wet dressings on the right palm and when she was seen one week later the lesion had begun to resolve.

Case 3. P. W., a 44 year old white man, did not ordinarily milk cows but on a few occasions about Thanksgiving of 1952 he "stripped out" a beef cow whose calf could not take all the milk.

He noticed a pin-head sized lesion on the dorsum of the index finger on November 28, 1952; when he was first seen December 12, the lesion was approximately 1 cm. in diameter. It was an elevated, dome-shaped, purple, nontender nodule which appeared to contain fluid but only a drop of serosanguinous fluid could be obtained on incision. Cultures of material from the lesion on blood agar and thioglycollate broth were negative and a small piece of tissue from the top of the lesion showed, according to the pathologist, "keratinized epithelium from the top of a blister."

Treatment consisted of potassium permanganate wet dressings and bacitracin ointment applied to the lesion. By December 23, the lesion appeared as a brown crust which was almost ready to drop off.

Case 4. D. P., a 38 year old white farm woman, had been milking cows for a number of years. A single nodule appeared on the left index finger on January 2, 1953, and the patient was advised to apply Aureomycin ointment on the assumption that the lesion was pyogenic. The patient was seen by us on January 15 because the lesion had failed to heal, and at that time it showed the typical features of milkers' nodule. The patient was not seen again but reported

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*The first two cases were reported briefly in 1952. They are reported in somewhat more detail here.

by mail on January 27 that the nodule had almost disappeared.

Case 5. J. B., a 31 year old white woman, was first seen on February 25, 1953. A lesion with the clinical characteristic of a milkers' nodule had been present on the right forearm for one week. Although the patient milked cows she had observed no lesions on the cows' teats or udders. On March 4, the lesion was still present and beginning to form a crust. The patient failed to return for re-examination.

Case 6. L. K., a 14 year old girl, was seen on November 6, 1953, because of an asymptomatic lesion on the right hand of three weeks' duration. The lesion was a typical, well-developed milkers' nodule about 1 cm. in diameter. The right epitrochlear lymph node was slightly enlarged and nontender. There was a scar from vaccination against smallpox in 1945.

The lesion was excised surgically and it healed per primum. Cultures from the lesion on blood agar, thioglycollate broth and Sabouraud's agar were negative. Microscopically the lesion presented the usual findings of milkers' nodule. Frei, Ducrey and tuberculin (1:1000) skin tests and the blood Wassermann and Kline were negative. Agglutinations for tularemia, brucellosis, typhoid and paratyphoid were negative.

The patient and her mother had been milking cows, and the mother stated that one of the cows had "pimples" on the teats three to four weeks earlier. On November 8 the patient's home was visited. No lesions of specific nature were seen on the cows' teats or udders, although one cow had a few crusts on two teats. Only the mother and daughter milked the cows and no new cows had been added to the herd for at least one year. The herd was composed of only eight cows and the farm was in the foothills of the Blue Ridge mountains in a rather isolated location.

Case 7. C. L., a 25 year old white man, had been

FIG. 1

(Case 7) Milkers' nodule on the second finger of the right hand.

FIG. 2

(Case 8) Milkers' nodule on the right palm. The lesion bears some resemblance to a pyogenic granuloma and malignant melanoma.

milking cows since September, 1953. During the first part of February, 1954, he noticed "pimples" that oozed sticky fluid on the teats of one of his cows. Approximately two weeks later (the last week in February) a lesion appeared on the second finger of the patient's right hand (Fig. 1), and on March 14 a second lesion was seen on the little finger of the left hand. The patient stated that by the time the second lesion appeared the cows no longer had lesions.

He was seen in the Clinic on March 17, at which time there were two typical milkers' nodules in the locations as mentioned. A small nontender epitrochlear lymph node could be felt on the left. There were two vaccination scars (boyhood and 1945) on the left upper arm. The larger milkers' nodule was biopsied and cultures made on blood agar, Sabouraud's agar and thioglycollate broth with negative results. The blood Wassermann and Kline were negative and agglutinations for tularemia, brucellosis, and paratyphoid A and B were negative.

The patient was seen again on March 26, because of secondary infection in the lesion on the second finger of the right hand. The lesion on the little finger had almost doubled in size. The patient was given systemic and topical antibiotics and instructed to return, which he did not do.

Case 8. R. H., a 41 year old farm woman, noticed a lesion on the right palm on March 2, 1954 (Fig. 2). A second lesion appeared on the right fifth finger on March 16, and a third lesion appeared a week later on the same finger (Fig. 3). Lymphangitis of the right arm and lymphadenitis of the right axilla resulted in admission of the patient to the hospital on March 23. The secondary infection subsided promptly with the systemic administration of penicillin and erythromycin. The patient was discharged from the hospital on April 2 and when she was last

FIG. 3

(Case 8) Milkers' nodule on the little finger of the right hand.

seen, on April 12, the lesions had regressed considerably. The patient reported by mail on June 1 that the lesions had completely disappeared.

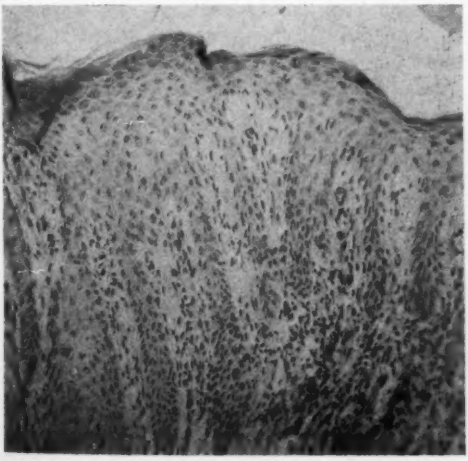
The patient milked one cow which had developed crusted lesions on the teats March 16. The teats were sore but otherwise the cow appeared well. The cow was milked by no one other than the patient and the patient had milked no other cows. On the farm there were four more cows which had not been milked. The five cows had been on the farm for at least four years and the only contact with outside cattle was the yearly trip to a neighboring farm for breeding purposes. The patient knew of no milkers' nodules among the milkers or cattle of the surrounding area.

The patient had been vaccinated approximately 30 years previously. She was vaccinated again April 2, 1954, and developed an immune reaction of four days duration.

Laboratory examinations in the hospital gave the following results: Microscopically, the palmar lesion and the larger one on the finger showed findings compatible with a diagnosis of milkers' nodule (Fig. 4). *Esch. coli* and bacillus proteus were cultured from the lesion on the palm. Frei, Ducrey and tuberculin (1:1000) skin tests were negative. Agglutinations for brucellosis, tularemia, typhoid and paratyphoid were negative as were, also, the Wassermann and Kline tests, and the urine and stool examinations. Examination of the blood showed 13.5 Gm. of hemoglobin, hematocrit of 43, and a total white blood cell count of 11,600 with 66 per cent polys., 29 per cent lymphocytes, 2 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils. The sedimentation rate was 26 mm. per hour.

The patient's cow was examined and the teats photographed on March 24, 1954. There were a dozen or more lesions on the teats. The lesions varied from 2 to 7 mm. in diameter and were composed of a brownish crust covering either a dry or a moist granulomatous base. The lesions tended to be round and resembled milkers' nodules in humans in the subsiding phase.

FIG. 4



(Case 8) Photomicrograph of lesion shown in figure 2. The peg-like prolongations of the prickle cell layer into the dermis and the granulomatous changes in the dermis can be seen. X 245.

Clinical Features

Milkers' nodules usually appear on the exposed surfaces of the milker. Persons who have been milking cows for a few days or a few months are most often affected, but the disease also occurs in those who have milked for a long time. Most of the lesions occur on the hands and forearms but they appear with some degree of frequency on the face and rarely upon other areas of the bodily surface. Most of the lesions arise on unbroken skin but some have appeared at sites of injury, such as cuts by wire or at the site of a calf bite. The incubation period between exposure to the affected cow and the appearance of the lesion may be as short as seven days.

The lesion first appears as a tiny, round, erythematous macule which soon becomes thickened to form a papule and slowly grows until it reaches the diameter of a centimeter or slightly larger. It attains its full size in approximately four weeks, remains essentially static for approximately two weeks, and gradually resolves without scar formation, the entire course of the uncomplicated lesion taking from six to eight weeks.

The mature lesion is usually round, sharply demarcated from the surrounding skin, and dome-shaped. Some of the lesions have a flat or plateau-like top. Frequently there is a

target or iris appearance to the lesion which is caused by a central gray area surrounded by alternating red and gray rings. The border is usually brighter red than the rest of the lesion. In the uncomplicated nodule the surface remains intact and although there is a suggestion of fluid content, incision is productive of only a small amount of serosanguinous material. On occasion the lesions assume a granulomatous appearance resembling a pyogenic granuloma, and at times the vascularity of the lesion and diapedesis of red cells produce a blue-black appearance not unlike that of malignant melanoma. Approximately 10 per cent of the nodules become secondarily infected, and in this circumstance regional lymphangitis and lymphadenitis often develop. Rarely the disease is complicated by an erythema multiforme-like rash.[5, 20] A second attack of the disease has been reported but this occurrence is exceedingly rare.[18]

One or two lesions are most commonly seen but it is not unusual for six to eight to appear and as many as eighty have been reported.[11] When large numbers of lesions are found the disease is usually not milkers' nodules but true cowpox (vaccinia), and laboratory studies will demonstrate the true etiology.

The lesions in the cow are variously described by patients and veterinarians as warts, pimples, scabs, crusts, vesicles and pustules on the teats or udders. Several lesions are usually present and, aside from local soreness which is evident when the cow is milked, the cow is not affected systemically. The disease in the cow lasts two to three weeks and it spreads slowly through a herd. Recurrences of the disease in a herd may occur but it is not clear whether a given cow may have a second attack.[24]

Microscopic Appearance

Microscopically, the epidermis of a milkers' nodule presents a considerable degree of hyperkeratosis and parakeratosis. The prickle cell layer becomes hypertrophic, at times to a pseudo-epitheliomatous degree, and there is a peculiar peg-like prolongation of the prickle layer into the dermis. Microscopic vesicles develop in some cases at the dermal-epidermal junction. There is a heavy dermal infiltrate of round cells and the small blood vessels show greatly thickened, hyperplastic walls.[2,4,7-10,12,13,15,17-23] The few descriptions of the microscopic features of the disease as it occurs in the cow indicate that the lesions are similar to those in man.[13,17,18]

Etiology

Milkers' nodules appears to be an infectious disease. The disorder practically always appears first in the cow, and man contracts it on the parts most exposed to the lesions on the cow (i.e., hands and forearms). The usual cultures for bacteria and fungi have not been helpful. To the best of our knowledge no studies to demonstrate spirochetes or leptospira have been done.

Most of the studies have included attempts to demonstrate a viral etiology. The pathology of the lesion suggests a viral cause, and there have been a few reports of inclusion bodies in the epidermal cells of the lesion, including two reports of inclusion particles seen on electron microscopy.[14,16] Attempts to transmit the disease by inoculation of tissue suspensions and fluid from the lesions to experimental animals have met almost uniformly with failure.[2,4,7,8,12-14,16,18,22] The occasional report of transmission of the disease has probably involved the virus of vaccinia, rather than the etiologic agent of milkers' nodule.[19,23] Veterinarians[24] have been unable to transmit the disease to cows and calves, and other investigators, including the authors of this paper, have failed to transmit the disorder to rabbits, mice and the chorio-allantoic membrane of the developing chick embryo.[15] In addition, we have been unable to demonstrate lesions in sheep after inoculation of material taken from milkers' nodules of three persons. Most of the experiments, including our own, involved storage of the material from the nodules before inoculating it into animals, which may be a factor in the negative results. Further studies are under way in our laboratory to identify the etiologic agent of milkers' nodules.

Discussion

In 1952, we predicted that milkers' nodules would be found more frequently in the South.[6] Since that time we have observed 6 more cases in Virginia and Garrison and Adams[10] have reported 14 cases in Tennessee. It is likely that the disease is much more common than realized, and as physicians be-

come familiar with the disorder, and the dairy industry expands in the South, more and more cases will probably be reported.

Four interesting features of our cases deserve re-emphasis. In case 1 the lesions presented only on the right hand, probably because the patient could milk only with this hand as the result of a previous cerebrovascular accident. The patient in case 3 apparently contracted his disease from a beef cow. The statement has been made that beef cattle do not have the disease but this may not be true. The teats and udders of beef cattle are not ordinarily inspected so that the disease in these animals may have gone unnoticed. Patients 1 and 7 had been milking cows a short period of time, which emphasizes the greater tendency of the person who has not been milking long to acquire the disease. Cases 6 and 8 occurred in milkers whose farms were quite isolated. These women did not milk other cows and no other workers milked their cows. It appears the disease was not spread to these cows by the milkers but rather that it appeared first in the cows from some unknown source and was transmitted from the cows to the milkers.

Summary

1. Six more cases of milkers' nodule have been added to our report of 1952.

2. The gross and microscopic features of the disease in man and cow have been presented.

3. The etiology of milkers' nodule has been considered briefly.

4. Special features of four of the cases have been discussed.

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Discussion (Abstract)

Dr. Howard Hailey, Atlanta, Ga. After reading Drs. Wheeler and Cawley's paper I spoke to an experienced veterinarian and asked him to tell me what he knew about milkers' nodules. He stated it was not a common condition, and that the use of electric milking machines would reduce the present incidence of the disease. Before the general introduction of electric milkers he had observed as many as six affected milkers in a single dairy at the same time. Further, it was a self-limited disease in cows and without any treatment the disease disappears in 10 to 14 days. He described affected hands in some milkers as a bilateral pustular eruption which he considered cowpox. I would want to rule out pustular pompholyx in these individuals so affected.

For about five years I milked cows morning and night, seven days a week. I cannot recall ever having seen a lesion on the teats or udder of a cow. "Sores," "dog day sores" and "dew poisoning sores" were common on the hands of children who came into town to attend school. Today, generally these lesions would be called, pyogenic granulomas or pyodermia.

An interesting point in this paper is that seven of the eight reported cases occurred during the rabbit eating season. I should like to have Dr. Wheeler tell us whether or not he recalls a seasonal tendency in the incidence of milkers' nodules reported by other authors on this subject. I am pleased to note that the agglutination test for tularemia was negative in all of the reported cases so tested.

Drs. Wheeler and Cawley are to be congratulated on a fine presentation of a condition which could occur in epidemic proportions in any section of the country.

Dr. Everett C. Fox, Dallas, Tex. Milkers' nodules is an interesting disease entity which has a rather characteristic appearance and course, and once it is observed other cases are relatively easily recognized. This demonstrates the importance of morphologic dermatology, since the diagnosis is usually established

on the basis of clinical appearance rather than laboratory or microscopic findings. An experienced clinician recognizes this disease, and when it is not recognized, considerable laboratory investigation may not reveal the correct diagnosis. Garrison and Adams found reports of only 20 patients with milkers' nodules in the American literature in 1953, and reported an additional 14 cases in Tennessee. Interestingly, three of these were related to the bite of a calf. The frequency of the lesions occurring on the fingers and hands with the history of contact with cows especially those having crusted lesions on the cow's teats or udder, aids in the establishment of the diagnosis. However, a single lesion about the face or lip would probably offer considerable diagnostic difficulty unless this diagnosis occurred to the examiner and a confirmatory history was obtained. We should appreciate Drs. Wheeler and Cawley's reminding us of this disease and its apparent increase in the South with increased development of dairying. Further viral studies are required to identify the causative organism and to further differentiate this disease from that of the virus of vaccinia. Natural cowpox should also be studied in relation to ORF (sheep pox).

I have enjoyed Drs. Wheeler and Cawley's paper and I believe it will make us all more conscious of this disease and increase our awareness of the increasing number of cases of milkers' nodules.

CASE REPORT

Myxoma of the Left Atrium

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The surgical removal of benign tumors from a heart chamber has been unsuccessful so far. However, preoperative diagnosis now being possible by angiocardiography, progress in operative technics will permit success at some time in the near future.

AUTHORS GENERALLY agree that tumors of the heart are rare, that most of these are metastatic and that most of the primary tumors of the heart are benign. They also agree that most of the benign tumors are myxomas which appear as pedunculated tumors in the left atrium. Diagnosis, heretofore difficult or impossible, now can be definitely established by angiocardiography which reveals filling defects in the heart chambers.[1, 2] Because of recent advances in cardiac surgery, these patients now may be cured. The main reasons for not considering myxomas in antemortem diagnoses have been the lack of knowledge about them and, more important, the common fault of not thinking of them. Therefore, we believe the following case report should be added to the literature.

Case Report

Dr. L. C. was admitted to the hospital on March 15, 1951, with the history that she had had no symptoms referrable to her heart until 10 days previously, when she became dyspneic. The dyspnea and later orthopnea gradually became worse. There was no history of pain, rheumatic fever or heart disease in the patient or family.

Physical examination revealed an orthopneic 69 year old woman. Her blood pressure was 165/105. The pulse was regular at a rate of 134. The eyegrounds showed grade II vascular changes. Her color was good. The neck veins were distended 2 cm. above the clavicles. The left border of cardiac dullness and point of maximal apical impulse were just inside the anterior axillary line. There were grade II mitral systolic and diastolic murmurs in the recumbent position. The diastolic murmur was accentuated in presystolic period. The first and second pulmonic sounds were accentuated. There were rales at both lung bases. The liver was down about one fingerbreadth and there was slight edema of the legs. The remainder of the physical examination otherwise was noncontributory.

She had recurrent leukocytosis throughout her hospital stay but numerous laboratory procedures did not aid in the diagnosis.

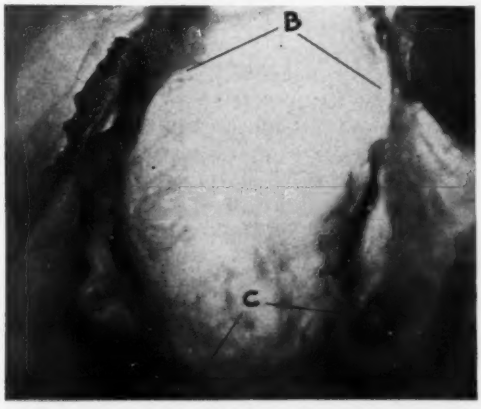
A *clinical diagnosis* was made of chronic rheumatic valvular heart disease with mitral stenosis and insufficiency and myocardial failure.

Course. By the second week after admission enough fluid accumulated in the left pleural cavity to require thoracentesis. It was necessary to repeat this procedure every three to five days throughout her hospital stay of seven months. Although her blood pressure returned to normal and her pulse rate slowed to about 100 immediately following therapy for myocardial failure, she was never appreciably relieved of her dyspnea except for a day or two following thoracentesis.

Within two weeks of admission, a progress note was made to the effect that the patient appeared sicker and was responding more poorly than she should with uncomplicated rheumatic valvular heart disease with myocardial failure. A malignancy was suspected and looked for but not found.

The unusually persistent and progressive myocardial

FIG. 1



Tumors exposed by removal of the lateral wall of the left auricle. (A) is a small myxoma with a narrow base; (B) shows the wide base of a large myxoma causing the signs and symptoms; (C) shows the tumor projecting into the mitral orifice.

failure was not related to changes in body position other than orthopnea expected with severe myocardial failure.

Autopsy. This revealed an unsuspected, large, firm, yellowish, polypoid tumor arising from the midportion of the interauricular septum in the left auricle and extending down to the mitral orifice (Fig. 1). It was 5 cm. in length and measured 3 by 2.5 cm. at its base. Another 1 by 1 cm. tumor of similar nature was found anteriorly near the entrance to the auricular appendage. There was slight thickening of the mitral valve. The left ventricle and the interventricular septum measured 12 mm. in thickness and the right ventricle measured 4 mm. Both auricles were moderately enlarged. The right pleural cavity was almost entirely obliterated by dense adhesions. Microscopic sections of the tumor consisted of stellate cells with a myxomatous type of stroma.

Comment. The hard, finger-like tumor with a wide base projecting into the mitral orifice no doubt maintained a relatively constant anatomic relationship to the orifice regardless of body position so that the signs and symptoms did not vary with changes in body position. However, the typical, intractable myocardial failure of rapid onset, responding poorly to digitalis, typical of myxomas characterized the clinical course of this patient. The recurrent left pleural effusion without associated right pleural effusion was accounted for by the obliteration of the right pleural cavity by adhesions.

Discussion

Investigators have generally agreed that tumors of the heart are rare and that malignant tumors are more frequent than benign. Lymburner[3] reported benign cardiac tumors in .05 per cent of all necropsies. Prichard,[4] reviewing the literature in 1951, stated that about 75 per cent of the primary tumors were benign and that about one-half of these were myxomas. Approximately 75 per cent of these were in the left auricle and 80 per cent were polypoid and usually attached by a pedicle to the foramen ovale or near it. Goldberg and associates,[1] in 1952, stated that 350 primary tumors of the heart had been reported to date. In 1953, Steinberg and associates[2] found that approximately 204 myxomas had been reported and added three of their own.

Most cardiac tumors diagnosed antemortem have been metastatic. However, a few primary tumors with antemortem diagnosis have been reported, several of which were sarcomas. To date, only six benign cardiac tumors have been diagnosed antemortem.[1,2,5-7] Four of these were intracardiac myxomas.[1,2,8]

The diagnosis of metastatic cardiac tumors has usually been made because of cardiac symptoms, or electrocardiographic, or x-ray changes associated with definite evidence of malignancy elsewhere. All primary malignant tumors were diagnosed because of cardiac symptoms associated with roentgenographic evidence of irregularities in the cardiac silhouette, electrocardiographic changes such as cardiac irregularities or conduction defects, or bloody pericardial effusion. The situation has been quite different in the case of benign tumors, especially intracardiac tumors. The first case of myxoma of the left auricle diagnosed on the basis of symptoms and physical findings was that of Kirkeby and Leren.[6] Actually, the diagnosis could only be suspected before the use of angiocardiography.[1,2]

As mentioned before, a most important point in the diagnosis of primary tumors of the heart is to think of the possibility. Some tumors cause few or no symptoms and are found incidentally at autopsy. Symptoms, of course, vary with the location and the size of the tumor. Prichard[4] stated that all tumors were large when causing symptoms. The tumors may occur at any place in the heart but occur usually in the auricles, especially in the left, where they often impinge upon the mitral orifice. Consequently, many authors have emphasized the similarity of myxoma of the left auricle to rheumatic valvular heart disease with mitral stenosis, or had diagnosed their own cases as such.[4,9-14] Several described peripheral emboli which raised the question of bacterial endocarditis.[4,14-16] Peripheral emboli may be caused by detached pieces of tumor or superimposed thrombi. The sedimentation rate frequently has been elevated but the blood cultures have been consistently negative.

The following important points in the differential diagnosis have been mentioned by many of the authors referred to above. The absence of a history of rheumatic fever is important, but probably has been overemphasized. Approximately one-half of the patients with rheumatic heart disease will not give the history of having had active rheumatic fever and one case of myxoma of the left atrium was reported in a patient with a positive history of rheumatic fever.[9] Frequently there is clinical evidence of mitral valvular disease because of mechanical obstruction of

the mitral orifice. Mitral diastolic murmurs with presystolic accentuation have often been noted, at times associated with accentuated apical first sound and pulmonic second sound. Variation of the diastolic murmur secondary to change in position has been emphasized repeatedly. The appearance of, or an accentuation of the apical diastolic murmur by the assumption of the upright position should be a clue to the diagnosis. The reverse findings are usually true in rheumatic valvular heart disease where the diastolic murmur usually appears or is accentuated in recumbency, especially in the left lateral position. Although 80 per cent of the tumors are polypoid, a tumor occasionally may have a broad base and maintain a relatively constant position so that the mitral murmur does not change with changes in body position.[9] Routine roentgen examinations often reveal enlargement of the left auricle, prominence of the pulmonary conus and occasionally enlargement of the right cardiac chambers. A change in symptoms with change in body position has also been stressed repeatedly. Occasionally dyspnea, palpitation, cyanosis, faintness, syncope, shock or even death occur suddenly with a change in position of the body because of mechanical obstruction to the blood flow through the mitral valve. Progressive intractable myocardial failure, usually associated with poor response to digitalis has been considered an important clue.

Although the possibility of clinching the diagnosis of an intracardiac tumor by showing a filling defect with angiocardiography was mentioned several times, it was not accomplished until 1952.[1]

Surgical removal of the intracardiac tumors was not attempted until 1952[1] although it was suggested previously.[8,11] Since then, two more operations have been attempted on patients with a positive preoperative diagnosis of rheumatic valvular heart disease with mitral stenosis.[7,9,10] A golf ball-sized tumor in the patient reported by Davis and Andrus[10] had a small base and was dislodged while being evaluated by the surgeon's finger. No operation has been successful. However, all operations have been done relatively early in the experience of the surgeons who all agree that surgical cures should be obtained. Bailey[7] thought his operations might have been successful had the tumors been approached directly.

Summary and Conclusions

(1) A case of functional mitral stenosis caused by a myxoma in the left atrium is presented.

(2) Symptoms were not altered with changes in body position, probably because the tumor had a broad base and maintained a constant position in relation to the mitral orifice.

(3) The findings which should lead to an early antemortem diagnosis are discussed. The most important of these are signs and symptoms of mitral stenosis which alter with changes in body position, and intractable heart failure.

(4) The importance of early diagnosis is emphasized because the only possible curative treatment is surgical removal of the tumor and this is most likely to be accomplished early.

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Diverticulum of the Female Urethra:

Report of 23 Cases with Adenocarcinoma in One*

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This lesion of the urethra will be found more frequently if a search is made for it. Its treatment by surgical removal is satisfactory.

THE WORD DIVERTICULUM COMES FROM THE LATIN, diverticulare, which means "to turn aside." Therefore, diverticulum of the urethra may be defined as a sac-like protrusion or a pocket that is continuous with the lumen of the urethra. A true diverticulum implies the presence of all layers of the urethra including a lining of epithelium. A false diverticulum or pseudodiverticulum connotes absence of one or more of the urethral layers and the absence of a mucosal lining. Since the epithelium may disappear from a true diverticulum as a result of ulceration, and since the diverticulum originally denuded of a mucosa may be lined by a proliferation of epithelial cells from the urethra proper, these designations have little or no meaning.

Urethral diverticulum in the past was considered to be a rather infrequent entity, but has become more and more commonly diagnosed in recent years. Wharton and Kearns[1] found only 30 cases in the records of Johns Hopkins Hospital between 1890 and 1949. Higgins and Roen[2] reported 7 cases in Cleveland Clinic in 22 years. Cook and Pool[3] reported 73 cases in the Mayo Clinic files as of 1948.

This report deals with 23 cases of urethral diverticulum of the female personally diagnosed over a period of six and one-half years of urologic practice which involves about 1,000 new urologic patients per year.

Etiology

Congenital diverticulum of the female urethra has been considered to arise from rupture of a congenital periurethral cyst or from a Gartner's duct or wolffian duct cyst. Acquired diverticulum in the female is ascribed to rupture of an acquired cyst of a periurethral gland or rupture of a periurethral abscess, or from trauma to the posterior wall of the urethra. Higgins and Rambousek,[4] in a report of 12 cases, stated that 11 of the 12 cases were definitely acquired.

Some of the predisposing factors to a urethral diverticulum would be habitual instrumentation, passage of urethral stones, intramural infections, electrocoagulation of urethral lesion, and trauma during labor. Histories of prolonged labor or the use of forceps have been quite frequently reported. Higgins and Rambousek have seen no cases in the nullipara.

In my own series, 10 were in the nullipara. Another had two pregnancies delivered by cesarean section. One case followed fulguration of a Skene's gland approximately two years before the diagnosis of diverticulum was made.

Congenital diverticulum is extremely rare and has been reported by Rioseco and Vargas[5] and Johnson.[6] Disontogenetic diverticulum of the urethra occurs in the form of ectopic ureter and this has been reported separately by Moore[7] and Willmarth.[8]

In the 23 cases being reported, 18 were in the white female, 5 in the colored. The age varied from 25 to 75 years, the majority falling in the third and fourth decades. Menville and Mitchell[9] reported the average age in their series at 38.8 years.

Symptoms and Signs

Clinical manifestations usually depend upon the size, location, depth of diverticulum, and also upon the presence of obstruction and infection. The usual symptoms in the female are dysuria, frequency, nocturia, hematuria, dribbling after urination, purulent urethral

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discharge, dyspareunia, occasional swelling in the vagina upon urination and pain in the urethral area on sitting. Two of the patients in this series had urinary retention in the course of their illness. Pelvic pain, pain in the flank and lumbar area are also mentioned. Wharton and Kearns[1] give the most common symptoms as frequency and burning present in 19 of 30 cases, pain in 12, incontinence in 9, straining in 7, hesitancy 6, dyspareunia 4, and retention 2.

The clinical findings are usually a vulvourethral bulging, a tender pulpaceous mass along the course of the urethra and a purulent or serosanguinopurulent discharge from the meatus upon palpation of the mass.

Pathology

Gross appearance. The diverticulum may vary in size from 2 mm. to 12 cm. in diameter, but the average is from 1 to 3 cm. It is accessible to palpation, usually seems to be rounded or saccular, soft and compressible so that the contents can be easily extruded; it is firm if the ostium is small and the contents trapped, and hard if filled with calculi. The opening may be single or multiple, pinpoint or as large as the diverticulum itself. It may be located anywhere along the course of the urethra. In the female it is most commonly found in the middle third. The lumen may contain urine, pus or calculous material. Wharton and Kearns[1] reported that 10 per cent of the patients in their series had calculi in the diverticulum. As many as 17 stones in one diverticulum has been reported. The lining membrane is usually smooth and gray, it may be ulcerated. The wall is of varying thickness and usually is irregular, thick, firm, and fibrotic. In the female the diverticulum may project to one side of the urethra, may encircle the urethra or may be in the midline and protrude superiorly beneath the internal sphincter and the trigone area.

Microscopic appearance. The urethral diverticulum may or may not be lined with mucosa. When present, the epithelium is either columnar, transitional or squamous cell variety. There are usually few or no muscle fibers within the wall and only rarely is granular tissue incorporated. Ordinarily the sac is composed of essentially collagenous tissue infiltrated with varying numbers of plasma cells, lymphocytes and monocytes.

Diagnosis

The diagnosis is made by four primary steps:

1. Palpating along the suburethral area and feeling a pulpaceous, tender mass in this area is helpful. Stripping the urethra towards the meatus causes a purulent discharge in a high percentage of cases.

2. Introduction of a sound into the urethra and bladder and palpating along the course of the sound will often indicate some mass between the urethra and vaginal layer.

3. Endoscopic examination. Using a No. 24 French McCarthy panendoscope or its equivalent to examine the urethral lining directly. A smaller panendoscope sheath does not distend the urethra well enough to visualize an opening in some of the cases. Palpation suburethrally during endoscopy is also of decided value.

4. Radiologic examination by either instilling dye into the urethra or by a voiding cysto-urethrogram will often indicate the presence of a diverticulum.

The cysto-endoscopic findings usually reveal a normal bladder. In the 23 cases reported here, the diverticulum was always in the middle or distal third of the urethra and distal to the external sphincter. The opening in the majority of cases was in the floor, just to the right or left of the floor. In no case was the opening found above the nine or three o'clock area of the urethra. Cook and Pool[3] reported two cases opening from the anterior urethral wall.

Differential diagnosis would necessarily include Gartner's duct cyst, although this cyst does not originate from the midline and is rarely infected and not tender. Bladder diverticulum, ectopic ureter entering into the bladder, abscess of Skene's gland, endometriosis with endometrial implants in the urethral area, gonorrheal urethritis, periurethral abscess, myomas, sarcomas, carcinomas and urethroceles all are to be considered.

Treatment

The treatment which has been used in the majority of the cases presented here has been

surgical excision. Several of the patients have not been operated on for one of several reasons. Sixteen had surgical excision of the lesion; 7 were not operated upon. Two were seen in the office on one occasion and did not return after recommendation for operation had been made. One patient was pregnant at the time of the diagnosis and was advised to have surgical treatment following delivery; she likewise was not seen again. One woman, 75 years of age, was not considered to be in a physical condition to undergo operation and was treated conservatively. Likewise, a second patient in the older age group was not pressed for a surgical procedure. Both of these patients had urethral dilatations and instillations of Argyrol, the sac was emptied on several occasions manually, and they were treated with antibiotics. Their results were quite satisfactory. Still another patient was operated upon by a local general practitioner.

The operative approach was a longitudinal vaginal incision directly over the diverticulum with dissection of the diverticulum as adequately as possible, and excision. The ostium to the urethra was closed with No. 38 gauge stainless steel wire on two occasions and the remainder of the cases with No. 000 chromic catgut. In some cases where the sac extended laterally and superiorly into the supraurethral and supravesicular areas it was impossible to completely remove the wall. One wall was removed as totally as possible in an attempt to prevent reformation of the pocket. Higgins and Rambousek[4] mention the cystoscopic cautery knife to enlarge the urethral opening to promote better drainage. Invagination of the sac by a series of purse string sutures is recommended, and Furniss[10] advocates electrocoagulation of the mucosa of the sac. The vaginal layer is then reapproximated with interrupted sutures. A catheter is inserted and left indwelling for approximately one week.

A number of these patients were followed by endoscopic examination after operation. One patient developed a urethrovaginal fistula immediately after her operation due to a perforation of the urethra with a suture in closing the vaginal layer in which an attempt was being made to control bleeding from the incision. This patient was not aware of the fistula, there was no incontinence and no further surgical treatment was recommended for the closure. In one patient, to be mentioned later, adenocarcinoma of the diverticulum was diagnosed, and approximately 8 months after the original operation a biopsy of the area was taken, and a fistula was created in an attempt to get adequate material from the wound area for study. The vaginal layer was closed with interrupted sutures but no attempt was made to redissect out the urethral opening for closure. A fistula developed in this case and, as in the previous one mentioned, no incontinence or distress occurred.

Recurrences of a diverticulum have been reported and stress incontinence may continue to be present after surgery.

I also had the opportunity to endoscope three patients who had had a diverticulectomy elsewhere. Two had healed completely and the third had a fistula. The patient with the fistula had some difficulty with recurrence of cystitis which was controlled easily with chemotherapy, but again this patient had no symptoms of incontinence or dribbling of urine.

There was, unfortunately, one death in this group of operative procedures. A 43 year old white woman developed shock two hours postoperatively without any explanation for this. She lived approximately 72 hours and expired in spite of all supportive measures. The autopsy findings were essentially negative. There was no hemorrhage in this case to explain the initial shock.

Adenocarcinoma of Urethral Diverticulum

E. S., 40 year old white office clerk, was first seen in the office on January 14, 1953, with the chief complaint of recurrent bladder infection of 6 years duration.

The onset of her illness 6 years before occurred with gross hematuria, frequency of urination with burning, lasting only a few days, and cleared spontaneously without medication. There was no history of fever associated with this illness. Since this illness she has had recurrent episodes of frequency with stress incontinence, low lumbar backache, but again without fever or other systemic symptoms. Three months before her first visit she had what she described as "virus infection." This cleared up, and one and a half months later she developed a recurrence of bladder symptoms again with burning, frequency, nocturia, but with no recurrence of hematuria.

The review of systems was negative; there had been no pregnancies, and the menses were normal. She gave

the history of bilateral salpingitis with double excision years ago; one ovary was removed at that time. Family history was noncontributory.

On *physical examination* the patient did not appear acutely or chronically ill. Temperature, pulse and respirations were normal; blood pressure was 130/80. The physical examination was negative with the exception of the genitourinary tract. The urethral meatus appeared normal. However, immediately proximal to the meatus vaginally there was a pulpaceous mass that was exquisitely tender to pressure; there was no cystocele or urethrocele. Upon pressing the mass there was a slight purulent discharge from the urethra. She also had a vaginal discharge. The cervix appeared normal and the rectal examination was negative.

Cysto-endoscopic examination revealed a normal bladder and the opening of the diverticulum in the left posterolateral urethral floor. Urethrogram was made.

The patient was admitted to the Good Samaritan Hospital on January 25, 1953. A *urethral diverticulectomy* under spinal anesthesia was done on January 26. She was placed in an exaggerated lithotomy position, prepared and draped for an incision in the superior vaginal wall. A No. 18 French sound was introduced into the urethral meatus and tilted down until the sound was introduced into the urethral diverticulum opening. The tip of the sound could be palpated immediately. A longitudinal vaginal incision was made for a distance of one and a half to two inches. The vaginal mucosa was separated from the underlying layer by sharp dissection and the diverticulum was exposed. In an attempt to completely reflect the vaginal mucosa, the diverticulum sac was perforated and a considerable amount of purulent material escaped. Sharp dissection was continued until the ostium of the diverticulum was identified. The sac was excised at this level. In removing the diverticulum a smaller pocket with a fistulous opening, which seemed to be draining urine, was just distal and closer to the urethral meatus, the opening being immediately below the meatus. This was also excised. There were two openings into the urethra. These were closed with purse string sutures of No. 000 chromic. A small portion of the excess vaginal mucosa was excised and the vaginal mucosa closed with interrupted No. 0 chromic. A No. 26 sound could be passed without encountering an obstruction.

A No. 18 Foley catheter was left indwelling for six days and then removed. The patient voided without difficulty and with excellent control.

The report of the pathologist on examination of the tissue removed was as follows: "*Gross.* These are numerous irregular fragments of somewhat membranous tissue averaging 2 cm. in diameter and 3 mm. in thickness. One surface appears to represent an inflamed mucosa with a thin fibrinous exudate present at some points.

"*Microscopic.* Some of the fragments from the wall of the diverticulum show a well-developed adenocarcinoma which appears to project into the lumen of the diverticulum in a papillary fashion, and also appears to invade the muscular wall. Only small foci of tumor are present, and many of the fragments contain no evidence of this lesion. One strip of connective tissue is lined by squamous epithelium reminiscent of vaginal mucosa, while others are lined by transitional epithelium typical of the urinary passages. The tumor cells line some of the membranous strips, and these cells appear different from the normal epithelium in being rather low with slightly enlarged nuclei and a rather helter-skelter arrangement. In some areas columnar epithelium containing secretory droplets is present and these appear somewhat atypical. It appears that the tumor actually arose in this type of epithelium, and we find continuity between tumor cells and the tall columnar epithelium, although the invasive portions of the tumor and the papillary portions do not show evidence of secretion and are arranged in small gland-like circles. This probably fortifies the view that adenocarcinoma of the urethra arises in the periurethral glands, as apparently do some diverticula. In this instance the course of events suggests that first a diverticulum arose in a periurethral gland, and second neoplastic transformation occurred in the epithelial lining.

"*Diagnosis.* Well-differentiated adenocarcinoma of urethra, presumably arising in diverticulum."

Course. She was then followed as an outpatient and was asymptomatic until approximately August 3, 1953, at which time she had onset of pain in the urethral region similar to that prior to her operation. Again there was no discharge, no fever and no chills. Physical examination at this time revealed a somewhat pale woman who appeared somewhat chronically ill. Temperature, pulse and respirations were normal; blood pressure was 118/70. The examination was negative except for the pelvic examination which again revealed a pulpaceous sensation along the suburethral area where the diverticulum had been excised vaginally. There was also one small area of granulation tissue in the diverticulectomy scar. There was a slight vaginal discharge which revealed *Trichomonas vaginalis.*

Cystoendoscopic examination revealed a slight opening in the urethra where the previous diverticulum ostium had been and pressure in this area produced a purulent appearing ejection into the urethra. No actual pocket was visible. In view of her previous diagnosis she was readmitted to the hospital.

Exploration of the previous vaginal operative wound was done. A No. 26 French sound could be passed without difficulty into the bladder. A small incision was made directly over the old incision. A specimen of the vaginal mucosa was excised. The incision was carried through the entire depth of the wound and also involved a small portion of the urethra. No attempt was made to close the urethral incision. The vaginal mucosa was reapproximated with No. 000 chromic sutures. Five radon seeds were implanted through the vaginal mucosa approximately 1.5 cm. apart. A Foley catheter was inserted and left indwelling. The five radon seeds contained a total of 14.95 mg. of radon.

The report of the pathologist was as follows:

"*Gross.* The specimen consists of tissue from the region of the vagina and urethra, which have been cut

into numerous small fragments in the process of making frozen sections.

"Microscopic. The tissue from the urethra abounds in fibrous scar tissue which is frequently infiltrated by a mononuclear type of chronic inflammatory type of epithelium suggestive of vaginal mucosa, but at one point we see a transition from this type into a stratified transitional type reminiscent of urethral mucosa. Small nests of epithelium in the submucosa may be representative of an epithelialized tract, or metaplasia of glandular tissues, the specific type of gland not being evident. We did not see at any point tissue which resembles the type of glandular epithelium found in the previous tumor, or any type of cancer cell.

"Diagnosis. Scar tissue with chronic inflammatory reaction."

The catheter was removed four days later and patient was able to void well. She was discharged the following day to be followed. Since this time she has been examined periodically, has continued to show the small fistula between the urethra and the vagina which has been asymptomatic. She has had no recurrence of cystitis, no bleeding and at no time any abnormal discomfort in the suburethral area.

She was seen on August 22, 1955, at which time endoscopic examination revealed papillary appearing tissue around the fistulous tract. This had more the appearance of urethritis cystica, or more as a single minute polyp. Biopsy was made and the report of the pathologist was as follows:

"Gross. Specimen consists of two small irregularly shaped bits of soft rubbery tissue of grayish white color; the largest measures aproximately 4 mm. in length, 1 mm. in width and 0.5 mm. in thickness.

"Microscopic. Sections show an extremely small fragment of tissue consisting of a loosely arranged slightly edematous connective tissue stroma overlaid by a transitional type of stratified epithelium. Extending into the stroma from the epithelium are a few glands of urethral type. The epithelial cells of these glands show some degree of atypicality in that a few of the cells are distinctly larger than others and possess enlarged hyperchromatic nuclei; these changes are seen only in scattered cells in a few areas and the basement membrane everywhere is intact and the full thickness of the epithelium is not involved.

"Diagnosis. Urethral mucosa and submucosa showing edema and a moderate degree of atypicality of some of the glandular epithelial cells."

Comment

Adenocarcinoma of the urethra is not too uncommon a finding. However, the usual tumor is an epithelioma of the urethra. In 1947, Walker and Huffman[11] reported 27 cases of adenocarcinoma of the urethra with an additional 5 instances which were of probable adenocarcinoma. These tumors usually arise from the floor of the urethra and along the midportion, seldom near the bladder neck. Adenocarcinoma arising in the diverticulum of the urethra is much less common. Hamilton and Leach[12] reported one case of adenocarcinoma arising in a congenital diverticulum; their patient gave a history of stress incontinence only, no history of trauma or infection of urinary tract. Just as in adenocarcinoma of the urethra, adenocarcinoma of the urethral diverticulum arises from the periurethral mucous gland. These patients are much more prone to hematuria and they also pass clumps of tumor material. Treatment recommended for adenocarcinoma of the female urethra is either excision of the urethra or radium alone, or radium followed by x-ray therapy. O'Conor[13] prefers thermal coagulation of adenocarcinoma of the female urethra since these tumors responded poorly to radiation.

Summary

In summary, 23 cases of diverticulum of the urethra are presented. This diagnosis is being made much more frequently today, because urologists and practitioners in general are becoming more cognizant of the disease and are keeping it in mind in their routine pelvic examinations. Several points are brought out which made the diagnosis of diverticulum more frequent, one being the routine stripping of the urethra towards the meatus, and watching for purulent urethral discharge from the meatus at the time of the stripping. Introduction of a sound into the urethra and palpating along the course of the sound in an attempt to delineate variations of thickness and consistency of the tissue between the urethra and the vagina are helpful. The routine use of a No. 24 French McCarthy Pan endoscope or some equivalent instrument will distend the urethra and permit better visualization of the urethra in routine cystoendoscopic studies. Also, the use of the urethral instillator introduced into the diverticulum opening and the instillation of radiopaque material into the diverticulum opening, or the use of a voiding cysto-urethrogram for diverticulum delineation aids in the demonstration of a sac.

Complications of diverticulectomy are brought out. A case of adenocarcinoma occurring in the urethral diverticulum is presented.

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Discussion (Abstract)

Dr. Maxwell A. Johnson, Tulsa, Okla. Dr. Brown has called our attention to an entity which seems to be diagnosed oftener the more one is aware of the possibility of its presence. The symptoms of this lesion are varied and not specific. Therefore one must routinely search the urethra, sometimes several times, in any woman who presents bladder symptoms. For this reason, as mentioned by Dr. Brown, we feel that careful study of each female urethra with the large panendoscope should always be done. Frequently it is only by following a tell-tale thin stream of pus back to its source that one can locate the orifice of a suspected diverticulum.

It is interesting to speculate on the probable origin of these diverticula. Dr. Powell of this city, in an as yet unpublished paper, recently offered a plausible sequence of events to account for these lesions and I should like to quote him as follows:

"A chronic periurethritis produced by a meatal stricture will cause abscess formation, which is at first microscopic and later macroscopic in size. These inflamed periurethral glands in the urethrovaginal septum gradually coalesce to form an urethral diverticulum. During urination hydrostatic pressure forces drops of urine into the diverticulum. The stenotic opening of this diverticulum alternately drains with relief of symptoms, or becomes infected, becomes occluded, and repeats the cycle of abscess formation."

Dr. Brown has mentioned excision of diverticula of the urethra through a vaginal incision. We have found this to be an excellent method and have adopted the plan of operation as suggested by Moore (J. Urol. 63: 611, 1952.) He uses a Foley catheter with the tip cut off to aid in the dissection. These drawings by Mr. William Didusch on this slide illustrate the method of Dr. Moore. You will note how he inserts the Foley catheter through a stab in the diverticulum and then uses the inflated bag to aid in the identification and dissection of the sac. Dr. Moore uses a purse string and reinforcing sutures to close the defect in the urethra and vaginal wall. In conclusion, I should like to congratulate Dr. Brown for bringing an excellent paper to us and to thank you for allowing me the privilege of discussion.

Dr. W. E. Kittredge, New Orleans, La. Just about everything that I had expected to say has already been said, and said very well. So about all I can do is to re-emphasize what I think are the important features of this problem.

First of all, the number of cases being recognized today has greatly increased over that observed a few years ago. Both urologists and gynecologists have become increasingly aware of the possibility of this disease and, therefore, have searched for it more diligently. Dr. Brown has said several times, and it cannot be overemphasized, that either a panendoscope or an endoscope is mandatory for inspection of the female urethra. Anyone who relies entirely on the right angle cystoscope for the examination of patients with urinary tract symptoms will miss a number of things, including diverticulitis, urethral carcinoma, and urethral polypi of sufficient size to be symptomatic.

To illustrate the increasing number of cases being diagnosed, I went over our cases at the Ochsner Clinic and on the Tulane Service at Charity Hospital in New Orleans; the total number of cases diagnosed in both institutions was 67 over a period of 33 years. Twenty of those were reported in the first 21 years and 47 in the next 12 years. In this series, incidentally, we found no instance of malignancy. There were three in whom a stone was present.

Forty-six of these patients were operated on with uniformly good results. There was no instance of either incontinence or fistula following surgery. Twenty-one were not operated upon since, as Dr. Brown says, there are instances in which common sense and judgment dictate conservative management, such as the old lady he mentioned, who is too old to justify an elective procedure of this kind. Furthermore, a number of the patients not operated upon were diagnosed on the Gynecology Service, at Charity Hospital, and were not referred to urology.

Another point is that the direct method of excision, as was so well shown in Dr. Brown's movie, has certainly served us well, and we have not been inclined to vary it, simply because we have had no trouble with it.

The only other variation in our experience that I can report is that we successfully repaired one postoperative fistula which had occurred elsewhere.

I again want to congratulate Dr. Brown on his complete presentation of the subject.

Dr. Eugene C. St. Martin, Shreveport, La. I am interested in this subject at present because I am in the process of preparing a short paper for the Louisiana State Urological Society next month, and I should like to compliment Dr. Brown on a very comprehensive survey of the subject.

Perhaps in Louisiana we are not as fortunate as you are in Oklahoma and Florida in having diverticula of the urethra which are of such size as to either put a sound into it from the urethra or to insert a

No. 16 5 cc. bag catheter. A patient was first seen about three years ago with a recent bout of left pyelonephritis, followed shortly thereafter by cystitis, and when I saw her she had pus in the urine. The x-ray studies of the upper tract looked good. I could not explain the pyuria, and pulling the panendoscope back into the urethra, I found this diverticulum. Subsequently I boldly started to excise this from below and two hours and fifty-five minutes later, we had completed the job. Putting the panendoscope in and out of the patient, it felt like the fellow who had a bad goose, that is, a goose 2 cm. off center. Finally, the job was done.

About a year ago I was referred a patient for reexamination who had had an attempt at diverticulectomy six years before, and there was apparently a recurrence. This was done by a gynecologist and the diverticulum was approximately the same size. Well, I was not so bold in attempting to repair this one. It occurred to me that if Dr. Coppridge could put an alligator forceps besides a panendoscope into the ureteral orifice, perhaps we could use something besides a panendoscope that would be of equal value.

As this slide shows I simply put a probe into the diverticulum, withdrew the panendoscope and left the probe in position, cutting over it. This operation only took 40 minutes.

This shows a very small diverticulum. I tried to make the opening bigger, and advised the patient to milk it out periodically. I do not think she did, and because of recurrent infection on three occasions, we excised it, using the same technic.

Here is another very small diverticulum. I have used this technic five times in the past year with very good results. It certainly makes the operation easier.

I thought I might just pass this on because I do not want you to get into the same problem that I have been in for two hours and fifty-five minutes.

Dr. Brown (Closing). I would like to thank Dr. Johnson, Dr. Kittredge and Dr. St. Martin for their comments. Also, I would like to agree with Dr. Johnson and Dr. Powell on the etiology of these diverticula in the female. I think that probably 99 per cent of them can be actually traced to previous periurethral abscess.

I just recently had a colored man with a huge diverticulum at the penoscrotal junction. Rather than open and excise it, I used a series of purse string sutures and just ablated the sac and it corrected the condition.

I would also at this time like to express my gratitude to Dr. Raines, Dr. Coplan, and the Houston urologists for their extensive efforts for putting on such a fine meeting.

Pre-employment Examinations in Small Industry*

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There are more employees in small industry than in big industry. The pre-employment examination is just as essential. The author details his practices in this field.

PREVENTATIVE MEDICINE IS THE LARGEST SINGLE BENEFIT we bring to the employee and management in industrial medical practice, and the first preventative measure is the preplacement examination.

The cardinal objectives of a preplacement physical examination are (1) to determine the person's physical qualification as to whether or not he is able to perform work without danger to himself or others; (2) to protect employees from contagious disease and unnecessary medical and industrial hazards; and (3) to protect the company from extra hazards through sickness or accident. The employee profits at the time he is hired by proper placement in a job compatible with his physical capacities and limitations, and from advice as to how, why, and when to correct defects which, when corrected, improve his health and increase his longevity, thus bringing benefits to him, his family, and his community. Management profits in that a higher morale is produced among the employees, better people are attracted to the plant, thereby giving a better selection of employees from which to build a good employee team, absenteeism and turnover is reduced, the productive life of the employees is extended, and accident costs and insurance costs are reduced. The quality, and productivity of the working force is improved. Through the examination, management has another channel of communication with employees. The organization is accepted more readily by the general public, and benefits from an industrial medical program go far beyond the plant itself. The preventive medicine program, of which the pre-employment examination is a part, is making an ever increasing contribution to betterment of industrial and health standards.[1]

Examination programs vary from company to company depending upon such factors as the number of employees, the availability of medical personnel, and medical facilities. Management must be thoroughly sold on, and enthusiastically support, and display keen interest in the pre-employment program before the employees accept the program wholeheartedly and before the vital object of gaining their cooperation can be achieved. Management must make it clear to the employees that the main purpose of the program is for their benefit, and management must understand that industry benefits only if the employees remain healthy and safe. To be successful the program must be a plant activity, and the plant doctor must come regularly to the plant to see and to be seen. He must be familiar with the plant working conditions, processes, and hazards before he is able to develop an effective and adequate program, with complete confidence of both employees and employer. The plant doctor is, therefore, an effective link in communication between employer and employee.

Large enterprises employing thousands of persons are commonly considered to be typical of present-day industry and business; actually two-thirds of the workers are employed in small plants. According to the panel's report to the President, of every 100 persons covered by social security, that is, workers in industry and commerce, and thus other than those in agriculture, or the self-employed, approximately 40 persons, or 40 per cent, work in plants employing less than 50 individuals, another 31 persons, or 31 per cent, work in plants employing 50 to 499. Thus, the small plant is still the major locale of employment

*Read before the Section on Industrial Medicine and Surgery, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

in this country, an important element in considering the industrial health programs.[2]

The pre-employment examination should not be used as a means for unjust exclusion, or to narrow the field of competition in employment. The man's ability rather than his disability must be the primary consideration at the time of the pre-employment examination. In considering the employee with some disability, we must remember that a properly placed disabled employee often is able to match production on a par with the non-disabled. When evaluating disability we must include those disabled both by injury and illness. We assume in the evaluation of the disability that, in most instances, the disability at the time of the pre-employment examination is the maximum, and that the disability will remain either stationary or will decrease. This is especially true in dealing with disabilities where injuries are concerned. In the case of disabilities due to disease the condition will be either stationary or static, will decrease, or will increase due to exacerbation of the disease. In this condition only a physician with good clinical judgment and a knowledge of job requirements can make a just decision.

The Examination

A confidential health record system is essential, and when we keep our medical information confidential, we gain confidence of the employee and do a better job in preventative medicine in our plant.

One of the most common mistakes the industrial physician or a private practitioner makes prior to a pre-employment examination is failure to get authority for the examination. "At any time that an industrial physician carries out a physical examination on a human being without authorization, written, oral, or implied, he is engaging in an illegal act of assault and battery and may become liable to legal complaint."[3] The principles governing the authorization of physical examinations are identical with that used for operations and treatment. It will prove desirable and beneficial to include in application forms for work a place for written consent for all appropriate, and reasonable physical examinations in connection with pre-employment, and it should include authorization for examination for subsequent re-employment as may be required in behalf of the employee and those working about him. The two authorization forms that we have and are using in our office are presented here:

Form I

Dallas, Texas Date.....

Name of Applicant .....

Date of Birth..... SS No. .....

I hereby make application for employment with ..... Company and agree to a thorough physical examination.

.....
(Applicant)

.....
(Witness)

Form II

Name of Applicant .....

Address .....
(Street) (City) (State)

Date of Birth ..... Sex ..... Race .....

I, ..., hereby give my consent to the performance of such examination upon myself as it may be deemed necessary by the industrial physician. I will in no way hold the doctor or doctors who perform the examination, or the clinic where the examination is performed, or the company requesting the examination responsible in any way.

.....
Signature of Applicant

As previously stated, the extent of pre-employment examinations vary from plant to plant. Most plants, with a rapid turnover of personnel, or where the employee is to do heavy work, are interested mainly in two things, the back and the hernia.[4] More extensive examinations are requested in plants where the turnover is slow, and for the more technical employee; here examination includes an extensive history, physical examination, and a comprehensive laboratory study.

Back injuries, alleged back injuries, and hernias present the most difficult and costly problems we have in industry today. In our pre-employment examination we make every effort to obtain a careful history and do a very careful physical examination for back injuries and hernias. An applicant for heavy

Form III

PRE-EMPLOYMENT EXAMINATION

Social Security No._____ APPROVED BY DALLAS INDUSTRIAL MEDICAL ASSOCIATION

Employer_____ Date of Examination_____

Name_____ Date of Birth_____ Sex_____ Color_____

Address_____ Marital Status_____ No. Children_____

A. Have you ever:

1. Received compensation for injury? Yes ☐ No ☐
2. Received Government pension? Yes ☐ No ☐
3. Received medical discharge from {Armed Forces} Yes ☐ No ☐
4. Received undesirable discharge from {Armed Forces} Yes ☐ No ☐
5. Been rejected for military service? Yes ☐ No ☐
6. Been hospitalized? Yes ☐ No ☐
7. Been operated on? Yes ☐ No ☐
8. Been rejected in any medical examination? Yes ☐ No ☐

B. Have you ever had disease or injury to:

1. Back, head, bones, joints or spine? Yes ☐ No ☐
2. Heart, lungs, kidneys, intestines, eyes? Yes ☐ No ☐
3. Rheumatism, diabetes, fits, fainting spells? Yes ☐ No ☐
4. Asthma, TB, high blood pressure, nervous breakdown? Yes ☐ No ☐
5. Excessive drinking, drug habit, or cancer? Yes ☐ No ☐
6. Rupture, varicose veins, syphilis, gonorrhea? Yes ☐ No ☐

C. If female:

1. Do you have a female disorder? Yes ☐ No ☐
2. Do you lose time from work because of period? Yes ☐ No ☐
3. Number of miscarriages. No._____
4. Date of last menstrual period_____ 19____

D. Two previous employments.

a._____ b._____

c. Why did you quit?_____

Explain above answers:_____

The above answers are true and correct to the best of my knowledge and belief. I understand that falsification is grounds for termination. This also authorizes release of any medical information concerning my past or present condition by any practitioner or hospital.

_____
(Signature of Applicant)

E. Examination: Temp._____ Pulse_____ BP_____ Height_____ Weight_____

2. Vision: Uncorrected, R 20/_____ L 20/_____ Near: R_____ L_____ Binoc. Vis. Yes ☐ No ☐ Color Vision: Nor. ☐ Abn. ☐
Corrected, R 20/_____ L 20/_____ Near: R_____ L_____ Visual Rating: Nor. ☐ Abn. ☐
3. Hearing: W.V. R 15/_____ L 15/_____ S.V. R 20/_____ L 20/_____

4. Deformities:	No ☐	Yes ☐	11. Heart:	Nor. ☐	Abn. ☐	17. Reflexes:	Nor. ☐	Abn. ☐
5. Skin:	Nor. ☐	Abn. ☐	12. Abdomen:	Nor. ☐	Abn. ☐	18. Extremities:	Nor. ☐	Abn. ☐
6. Hygiene:	Nor. ☐	Abn. ☐	13. Hernia:	No ☐	Yes ☐	19. Varicosities:	Nor. ☐	Abn. ☐
7. EENT:	Nor. ☐	Abn. ☐	14. Genitalia:	Nor. ☐	Abn. ☐	20. Back:	Nor. ☐	Abn. ☐
8. Head, Neck:	Nor. ☐	Abn. ☐	15. Varicocele:	No ☐	Yes ☐	21. Venereal Disease:	No ☐	Yes ☐
9. Breasts:	Nor. ☐	Abn. ☐	16. Hydrocele:	No ☐	Yes ☐	22. Enlarged Nodes:	No ☐	Yes ☐
10. Lungs:	Nor. ☐	Abn. ☐				23. Rectal Exam.:	Nor. ☐	Abn. ☐ (Optional)
						24. Pelvic: Exam.:	Nor. ☐	Abn. ☐ (Optional)

REMARKS:_____

F. LABORATORY WORK:

Urinalysis: Sp. Gr._____ React_____ Alb_____ Sug._____ Micro_____

Optional: RBC_____ Hb_____ WBC_____ Diff._____

Stool_____ Serology_____ Other Lab Work_____

X-Ray Chest ☐ Lumbar Spine ☐ Other_____

G. PHYSICAL CLASSIFICATION:

1. Employable ☐
2. Employable with minor defect ☐
3. Employable for specific job ☐
4. Rejected until defect corrected ☐
5. Rejected ☐

REMARKS:_____

_____ M. D.

ICC CERTIFICATE:

DOCTOR'S CERTIFICATE

This is to certify that I have this day examined_____ in accordance with S191.2, and the physical examination procedure prescribed by the Motor Carrier Safety Regulations, Revision of 1952, of the Interstate Commerce Commission, and that I find him

Qualified only when wearing glasses ☐ Qualified under said rules ☐ Not qualified to drive ☐

I have kept on file in my office a completed examination form for this person.

_____ (Date) _____ (Place) _____ (Signature of Examining Doctor)

Signature of Driver_____ Address of Doctor_____

Address of Driver_____

A. OBJECTIVE OF PHYSICAL EXAMINATIONS:

1. To determine a person's physical qualifications as to whether or not he is able to perform work without danger to himself or others.
2. To protect employees from contagious disease and unnecessary medical and industrial hazards.
3. To protect the company from extra hazard through sickness or accident.

PHYSICAL CLASSIFICATION RATING:

1. **Employable.** Physically qualified for any type employment. Has no physical defects.
2. **Employable with minor physical defect.** Under this classification are those with physical defects which do not handicap the employee from doing any type of employment.
3. **Employable for specific job.** Such as clerical, sedentary or other work compatible with his physical condition. This rating may be used for an applicant with slight deformities or other defects which would disqualify for 1 or 2 rating but do not warrant a 4 or 5 rating.
4. **Rejected until defect corrected.** Disqualified for employment but may be reconsidered when defects are corrected. Such defects as acute venereal disease, contagious diseases, other diseases, serious defects of teeth or gums, hemorrhoids, active pilonidal cyst, fissure or fistula, hydrocele, hernia, pterygium, cataract, blood pressure over 160/100, 25% over or under weight, vision with or without glasses 20/30 in one eye and 20/40 in the other eye and minor urinary infection.
5. **Rejected or physically disqualified for employment in any capacity. This rating must be used whenever a physical defect makes the applicant unfit for employment and makes him an extra hazardous or accident risk.**

physical work, work that requires continuous lifting of material weighing over 25 pounds, or an equivalent of pulling or pushing, is examined in the following routine fashion:

Examination of the back is done by standing behind the employee who is in the erect position. The extent of lordosis, symmetry of the lumbar angles, deviation of the spinus process laterally, the level of the scapulas, and the level of the iliac crests are noted. The employee is then asked to bend to the right side with the legs straight, the spine is inspected for areas in which bending is limited; he is then asked to bend to the left and the spine is again inspected for limitation of bending. Standing to the right and then to the left of the employee, the normal curves of the cervical, dorsal, and lumbar regions are observed, and any deviation from normal contour is noted. The examiner observes from the side as the employee bends from the hips, and notes that in the normal spine, flexion is throughout the length of the spine; if any deviation from flexion throughout the entire length of spine is noted, this is recorded. The patient is then placed in the supine position, and the straight-leg-raising test is performed, and any abnormality here is noted.

In the examination of hernias, all types are looked for, the inguinal, femoral, ventral, umbilical, and postoperative. A digital examination is done for inguinal hernias and for undue patency of the inguinal canals. The employee stands with the feet well apart, the toes pointing in and the heels pointing out, and then rising on the balls of his feet, with his arms above his head, he coughs.

From November 1, 1954, to October 31, 1955, we have done 1,055 pre-employment examinations of all types, that is of employees doing light work or office work, and of employees doing manual or heavy labor. Of this number we have disqualified for employment 11 applicants because of their back, and 24 applicants because of hernias of all types, or approximately 1.1 per cent, and 2.4 per cent respectively.

Employees usually think that the less you know about them the more likely they are to be accepted for the job, therefore, thoroughness is essential in the history and physical examination. A good history in a pre-employment examination is as essential or even more essential than in clinical medicine.

A careful check is usually made of the employee to find out about his service status. If he is a veteran, he is usually checked for a history of tropical diseases, a history of nervous disorders, and the type of discharge he received. If he received a disability discharge, the cause for this is determined. If he was of service age and was not in the service, his selective service classification is requested. If he was IV-F under selective service, the reason for this is desired.

As you see in the "Vital Statistics" of Form III preceding the history, the Social Security No. is obtained; this never being changed is positive identification of the employee. Time will not permit us to embellish each point or question in this history. The history form in the upper portion of the pre-employment examination presented here, and which is approved by the Dallas Industrial Medical Association, is simple, and I believe covers most points we look for in our occupational history.

At the completion of the pre-employment history, there is a statement to be signed by the employee indicating that his answers are true and correct to the best of his knowledge. This should be signed in the presence of the examining physician.

The physical examination form which I present here, and which is approved by the Dallas Industrial Medical Association and is used by this organization, is similar, I am sure, to the form you are now using. We have found after using numerous and varied examination forms, that this one probably is more practical. The time saved in recording the findings, or in the "paper work," can be used in doing the actual examination. The urinalysis is routine, and other laboratory procedures are optional depending upon the type of job. Time will not permit the showing or reading of the numerous history and physical examination forms, that have been used, and are still being tried.

In doing the examination, males are examined in strict privacy with only the employee and the examining physician present. A trained nurse is present with the examining physician when a female employee is examined.

Evaluation of the Applicant

At the completion of the pre-employment history and physical examination, an evaluation of the applicant is made for proper job placement. His physical classification rating is determined:

Physical Classification Rating:

1. *Employable.* Physically qualified for any type employment. Has no physical defects.

2. *Employable with minor physical defect.* Under this classification are those with physical defects which do not handicap the employee from doing any type of work.

3. *Employable for specific job.* The work may be clerical, sedentary or other work compatible with his physical condition. This rating may be used for an applicant with slight deformities or other defects which would disqualify for a 1 or 2 rating but does not warrant a 4 or 5 rating.

4. *Rejected until defect corrected.* This disqualifies the applicant for employment but he may be reconsidered when defects are corrected. Such defects may be acute venereal disease, contagious diseases, other diseases, serious defects of teeth or gums, hemorrhoids, an active pilonidal cyst, fissure or fistula, hydrocele, hernia, pterygium, cataract, a blood pressure over 160/100, 25 per cent over or under weight, vision with or without glasses 20/30 in one eye and 20/40 in the other eye, and minor urinary infection.

5. *Rejected or physically disqualified for employment in any capacity.* This rating must be used whenever a physical defect makes the applicant unfit for employment and makes him an extra hazardous or accident risk.

At the bottom of the examination form there is a doctor's certificate which is to be completed in the case of all interstate drivers. It is required that a copy of this form be filed in the carrier's office, and also that the driver keep on his person at all times while driving, a copy of this certificate.

Summary

In summarizing, I wish to point out that the first preventative medical measure in industry is the pre-employment examination. The employee as well as management profits by the pre-employment examination.

Approximately 71 per cent of workers in industry and commerce work in plants employing less than 500 employees.

An applicant for a job who presents a disability deserves extreme care in the evaluation of his disability and the indiscriminate disqualifying of a disabled man is taboo.

A common mistake of the examiner is the failure of obtaining written permission from the employee prior to the pre-employment examination. A more careful history and physical examination for back injury and for hernia is required in small plants with rapid turnover of personnel. We have disqualified 1.1 per cent for back difficulties and 2.4 per cent for all types of hernia over the last 12 months.

Our preference for a pre-employment history and physical examination is a "check in type" which permits checking in a column, "yes" or "no" or "normal" or "abnormal" rather than a "write in type." This saves time and "paper work;" the time saved can be used in doing a more thorough history and physical examination. This "check in type" has been recomended by the Dallas Industrial Medical Association, and some 15 industrial doctors in the Dallas area are using this type of examination in the small plants in which they do pre-employment examinations.

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Discussion (Abstract)

Dr. Joseph M. Bosworth, Atlanta, Ga. Thank you, Dr. Payne, for this very excellent paper. I think you have covered the subject exceedingly well, and I would like to make two comments, if I may. First, I am delighted to hear that a county medical society has adopted a form for examination. I have not seen this anywhere else yet. This is quite enlightening to me. I think it is a healthy trend and I would like to see more of it.

Secondly, I like your emphasis on examining the patient rather than so much writing. I think one of the biggest mistakes I see, when I talk to doctors about doing examinations, is that they are always interested in the form and very seldom ask about what to do in the examination. I think forms can confuse doctors, and I am delighted to hear that you are giving examinations of patients with their overcoats off. I have

seen too many instances where doctors can do a very beautiful examination on paper with overcoats on. I myself was examined, when I went to work with my company, by a very reputable doctor, incidentally, and I never even took off my coat, much less anything else. In the school I attended, we had to have people undress for examination. It may be that some of the more modern doctors can examine persons with the overcoats on, but I did not learn it that way. The examination of the patient is essential rather than so much time spent on paper work. Paper work is relative.

Dr. W. M. Wallis, Houston, Tex. I have a question I would like to ask both Dr. Payne and Dr. Bosworth. I have no difficulty in correlating the medical history among the veterans who are discharged, but when the question comes to their Selective Service classification, there is a wide variation, and a large number of them state that they are IV-F. However, they do not know why, and there is no apparent reason. How do you obtain the information from the Selective Service Boards?

Dr. E. F. Buyniski, Cincinnati, Ohio. I think Dr. Payne has done a very splendid job in recognizing the problems in the preplacement examination. I have two questions I would like to ask him. One is how long an interval do you allow to elapse between the time that you examine an applicant and the time that you take legal action on this little phrase that you included in the examination that "I hereby swear that this is true." In other words, suppose that three years after employment a situation arises where a man develops an acute psychosis, for example, and it gets to be a very complicated employee relations problem, and then you question him and he says, "Oh, Doctor, I was hospitalized five years ago for this." Do you fire him on the basis of falsification of medical records?

The second question I would like to ask Dr. Payne is, do you inform the applicant of the defects you find, and if so, how do you handle a case of, for example, obesity, or where a person has a marked severe anxiety neurosis or has a specific paranoid personality?

Dr. Ed Norfleet, Sapulpa, Okla. I would like to ask Dr. Payne on what basis did he disqualify these men as to back. He had quite a large percentage, and I would like to know if you might briefly summarize how you did this in your office, and get such a high number of disqualifications for backs?

Dr. Payne (Closing). In answer to the first question, on the difficulty of obtaining information from the Selective Service Boards, where the applicant does not know the exact reason for his classification as IV-F, after a very thorough and careful examination I write a letter to the Selective Service Board and request the applicant for employment to take the letter to the Army Induction Center, or the Selective Service Board and attempt to obtain the reason for the IV-F classification. My letter usually reads something like this:

Date: .....
Selective Service Board No. 2
Dallas, Texas

Re: Mr. John Doe
Date of Birth
Selective Service No. .....
Dallas, Texas

Gentlemen:

The above named person was given a pre-employment examination on this date and he informed us that he was classified as IV-F under the Selective Service Act. The exact cause for the classification IV-F was not known and was not determined. We, therefore, disqualified this person for employment until the exact reason for his IV-F classification can be determined. Your assistance in this case will be greatly beneficial and appreciated and will be treated strictly confidential.

Trusting to hear from you at your earliest convenience, I remain

Very truly yours,

..... M.D.

Following my signature, I have the pre-employee then sign the following statement.

Date: .....

I hereby authorize you to furnish the above named Doctor any and all information he desires concerning my past or present health history.

.....
(Employee)

I have considerable trouble getting information from the Selective Service Board at times. If I cannot get the information as to the reason why the pre-employee was IV-F, I reconsider his entire pre-employment history and examination and attach some physical classification.

The next question related to the statement that the applicant signs at the end of his careful pre-employment history, namely "I understand that falsification is grounds for termination." Most of the companies I do pre-employment examinations for set a time limit of 60 days, and a few 90 days. I have had no legal complications over any terminations of employment. Terminations of employment are very rare. I discourage the time limit being set longer than 90 days.

As far as the question of obesity, neurosis and psychoneurosis is concerned, I usually sit down with the applicant and have a discussion with him and make recommendations in writing. I have a form I use which reports the defects found. This they take to their family physician. The form that I use is as follows:

Date: .....

The recent (pre-employment) (periodical) examination of Mr. .....
(employee)

resulted in finding the following defects:

It is suggested that you consult your personal physician for proper correction and treatment. A complete copy of your examination will be submitted to your personal physician upon his request.

It is requested that you sign below to indicate that you have been advised of the above findings.

.....
(employee)

.....M.D.
(examiner)

I believe you will find forms very similar to this one in different Industrial Medical books you may have. A new and excellent book, which I have just finished reading, is "Modern Occupational Medicine" by A. J. Fleming, C. A. D'Alonzo and J. A. Zapp. It has some very good forms.

The next question has to do with the type of examination I use in the examination of backs. I have this information in the paper, but because of the shortness of time did not go into back examinations in detail. If you would like for me to take the time now to read this I will be very glad to do so. (These sections were read as they appear in the paper).

ARE YOU MOVING?

Please send the following to: Southern Medical Association

1020 Empire Building, Birmingham 3, Alabama

Name.....
(Please print)

Old Address:

Street.....

City and Zone.....

State.....

New Address:

Street.....

City and Zone.....

State.....

CASE REPORT

Diffuse Interstitial Fibrosis of the Lungs (Hamman-Rich Syndrome):

A Case Report with Pulmonary Function Studies

JOSEPH M. MERRILL, M.D., JAMES J. CALLAWAY, M.D., and GEORGE R. MENEELY, M.D.,† *Nashville, Tenn.*

A RAPIDLY FATAL FORM of diffuse interstitial fibrosis of the lungs was described by Hamman and Rich in 1935.[1] The clinical and pathologic features have been emphasized in subsequent case reports.[2-17] Studies of pulmonary function in this disease are difficult, and the previously reported cases contain few such studies. This lack of previously reported cases with pulmonary function studies prompted the present report.

Case Report

S. C., a 31 year old white man, entered Thayer VA Hospital with cough and dyspnea for 27 months. These symptoms followed a minor upper respiratory infection and persisted without remission during his illness. There was precordial pain on exertion, relieved by rest. Orthopnea and weight loss occurred and hospitalization was required because of the severity of the complaints. A diagnosis of chronic pulmonary fibrosis of undetermined etiology was made. Treatment was ineffective and because his symptoms progressed, he was transferred to this hospital.

Physical examination showed a well-developed, but acutely and chronically ill man. He was dyspneic with intense cyanosis of the lips and nail beds. There was marked clubbing of the fingers. The anteroposterior diameter of the chest was increased with limitation of motion bilaterally. Loud, coarse, and musical rhonchi were heard throughout the lung fields. The heart was normal in size and there were no murmurs although the second pulmonic sound was accentuated. The remainder of the physical examination was not remarkable.

Laboratory Data. The white blood count was 10,200, with neutrophils 58 per cent, lymphocytes 35 per cent, monocytes 4 per cent and eosinophils 3 per cent. Hemoglobin was 14.8 Gm. per 100 cc., hematocrit 48 per cent and E.S.R. 10 mm. per hr. (Wintrobe). Urinalysis was negative. The VDRL test was negative. Blood chemical studies showed N.P.N. 52 mg. per 100 cc., CO_2 20 mEq., chloride 70 mEq. serum, albumin 3.0 Gm. and globulin 2.5 Gm. per 100 cc., serum sodium 136 mEq. and potassium 3.5 mEq. Second determinations were CO_2 25 mEq. and chloride 91 mEq. Sputum for acid-fast organisms and a Papanicolau smear for tumor cells were negative. The chest x-ray was interpreted as follows: "the entirety of both lung fields is involved in an interstitial fibrosis of minimal to moderate degree." The electrocardiogram showed changes typical of right ventricular strain and hypertrophy. Pulmonary function tests: the ventilatory and blood gas studies were performed nine days before death. The results are seen in tables 1 to 3.

The patient's course in the hospital was marked by progressive dyspnea and orthopnea. This was accompanied by severe generalized chest pain. Throughout his hospital stay the temperature ranged between 100° and 103° F. He expired 14 days after admission.

Autopsy. The outstanding features on postmortem examination were limited to the heart and lungs. The right lung weighed 810 grams and the left lung 770 grams. They were firm and remained expanded when

TABLE 1

Total vital capacity (ml.)	1935
3 Second vital capacity (ml.)	840
Maximum breathing capacity (L/min.)	68.33
Breathing reserve (L/min.)	59
Air velocity index	1.8
$\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$	86%
Resting minute ventilation (L/min.)	9.33
Oxygen consumption (ml./min.)	281
Oxygen removal ratio	30

TABLE 2

Functional residual capacity	1298 ml.
Expiratory reserve volume	421 ml.
Residual volume	877 ml.
Inspiratory capacity	974 ml.
Total lung capacity	2272 ml.
Residual volume total lung capacity ratio	38%

†From the Research Laboratory, Thayer VA Hospital, and the Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.

TABLE 3

*Arterial Blood Gas Analyses:**	*Room Air*	*100% O_2***
Oxygen content (Vol. %) (resting)	15.63	20.19
CO_2 content (Vol. %)	42.49	43.53

*Analyses done on Van Slyke manometric apparatus.

**After breathing 100 per cent oxygen by mask for fifteen minutes.

removed. There were innumerable subpleural blebs. Sections of the lungs revealed numerous cysts varying in size from pin-point to 0.75 cm. in diameter. The apices were dark red in color and had the consistency of skeletal muscle. The tracheobronchial lymph nodes were moderately enlarged. The heart weighed 350 grams and the volume of the right ventricle was approximately two and one-half times its normal size.

Microscopic study of the lungs showed dense thickening of the alveolar wall with the formation of a hyaline membrane. In addition the alveolar walls showed mononuclear cell infiltration. The peripheral portion of the lungs showed marked fibrous changes with dilatation of the alveoli. These were lined with tall columnar ciliated epithelium and in a few areas squamous metaplasia had taken place.

Discussion

In the original description of this disorder, the fulminant and rapidly fatal features were emphasized. Subsequently, cases of a more chronic variety have been described. Dyspnea, which is usually progressive but may be remittent, is the predominant symptom. The onset frequently follows a mild upper respiratory infection. Dull chest pain or a sensation of tightness in the chest associated with palpitation is not unusual. Weight loss and night sweats are infrequently seen. The physical examination usually shows signs of air hunger, cyanosis, clubbing of the fingers, and rales and rhonchi of varying intensity and quality scattered throughout the chest. Laboratory data other than blood gas analyses and pulmonary function studies are not particularly helpful.

Pathologic studies have revealed that the significant abnormalities are limited to the contents of the thoracic cavity. The lungs are heavy with a rubbery consistency. Areas of consolidation and areas of emphysema are interspersed throughout the lung parenchyma. Fibrous adhesions in the pleural and pericardial cavities are occasionally seen. Marked proliferation of connective tissue is found in the alveolar wall and a hyaline membrane frequently lines the alveoli. There is no organizing exudate in the alveoli although macrophages and giant cells may be found in the air sacs. Dilatation and hypertrophy of the right ventricle is usually seen.

Pulmonary function tests in interstitial fibrosis of the lungs show: (1) decrease of total lung capacity; (2) decrease of vital capacity; (3) decrease in maximum breathing capacity; and (4) impairment of the transfer of oxygen across the "alveolocapillary membrane." The most striking features in the pulmonary function tests on this patient were: the loss in total vital capacity, the reduction in total lung capacity with a slightly increased residual volume-total lung capacity ratio, and the low arterial oxygen content which rose on the administration of 100 per cent oxygen by face mask for 15 minutes.

Summary

A report of a patient with the Hamman-Rich syndrome who had clinical and pathologic features typical of this disorder is presented to illustrate the disturbed pulmonary function in this disease.

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Sciatic Tension Test*

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A new test is described to differentiate between the pain of pressure on nerve roots from that due to other mechanisms in the lower back.

THIS IS A NEW CLINICAL TEST devised by one of us (W.M.D.) to demonstrate the presence or absence of nerve root pressure as the causative agent in back and leg pain. It allows the examiner to differentiate the pain of root compression from other causes of low back pain and sciatic, even in the earliest stages.

Anatomic Considerations

A brief review of the anatomy and nerve supply of the area will make this test clearer. The dura with the nerve roots lies in the spinal canal. The nerve root leaves the spinal canal by way of the intervertebral foramen, which is bounded anteriorly by the disk, posteriorly by the pars interarticularis, the interfacet joints and to a certain extent by the ligamentum flavum, and superiorly and inferiorly by the pedicles. The sensory supply to the dura is the meningeal branch of the spinal nerve, and the sensory supply to the remaining structures of the back, including joints, muscles, fascia, subcutaneous and the skin, is the posterior ramus of the spinal nerve.

Low back pain and sciatica may be produced by 2 mechanisms: (1) the root compression syndrome usually originating in the region of the intervertebral foramen; and (2) irritation of the nerve endings of the posterior rami or meningeal nerves.

If the pain in this latter category radiates over the sciatic area, it is a referred pain. This second type, due to irritation of nerve endings, includes any inflammation, injury or pathologic process in the low back area. Typical causes are traumatic myositis, fascitis or sprain of the facet joints. In the early stages of disease of a disk, pain may be caused by irritation of the nerve endings in the posterior longitudinal ligament.

Pain caused from root compression may result from any encroachment on the nerve root. The most frequent cause is disease of a disk or injury sufficiently advanced to cause direct pressure on the nerve root. Root compression may result from any process that decreases the size of the intervertebral foramen, such as sprains of the interfacet joints with swelling, pressure from enlarged cartilagenous or bony plaques in the defective area in the cases of spondylolysis or spondylolisthesis.[1,2] Arthritis in the acute stage with swelling, and in later stages with actual spur formation, will encroach upon the nerve root. In all cases of the root compression syndrome there is an element of edema, either in the nerve root or in the encroaching pathologic process, or both.

Differential Diagnosis

The prognosis and treatment of low back pain will follow a more accurate pattern if we can differentiate nerve root pressure from the other causes of pain. This new test will make this distinction more accurately than any other test and approaches 100 per cent accuracy in predicting cases of nerve root pressure, later demonstrated at operation (Table 2).

It was reasoned that the test, to be specific for nerve root pressure, must be one in which there was no movement at the time the test was performed, as this movement may produce pain and limitation by irritation of nerve endings in the back and thereby the pain may be the result of local or referred pain. Straight-leg raising test with Lesague's modifications causes motion in the back and is therefore not selective for nerve root pressure. The principle of producing tension on the sciatic nerve and its roots by pressure over the popliteal space was demonstrated by Cram.[3] The specific test he advocated, however, was not entirely satisfactory in making the distinction between nerve root pressure and other causes

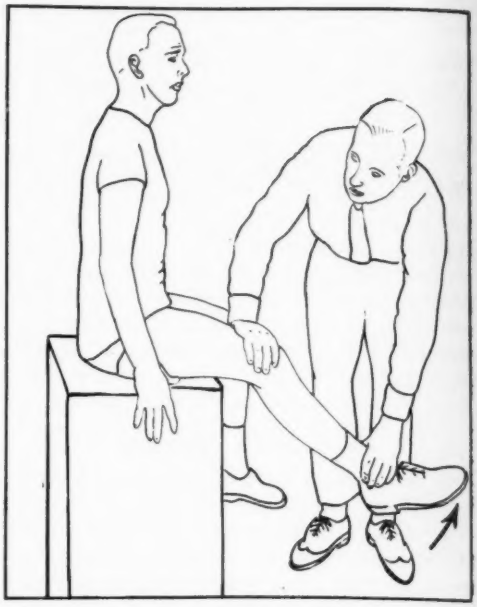
*Read Before the Section on Orthopedic and Traumatic Surgery, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

of pain. It was difficult to execute even with an assistant holding the leg in a straight-leg raising position. There was some movement transmitted to the leg in making pressure over the uplifted knee. Efficient pressure could not be applied to an absolutely immobile leg and body. The recumbent position eliminated the weight of the body forcing downward against the disk, thereby decreasing the sensitivity of the test. The recumbent position also made variation in body position difficult. It was not feasible to place the patient in various positions (Fig. 1) in order to place the nerve root in a position of a maximum vulnerability to pressure just below the tolerable pain threshold.

Technic of Sciatic Tension Test

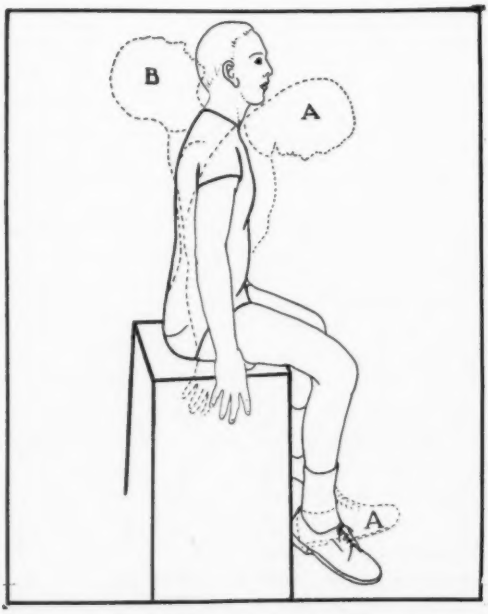
This new test has the weight of the body forcing downward on the disk and allows for multiple positions to place the nerve root in its position of maximum vulnerability (Fig. 1). It allows the examiner without an assistant to maintain absolute immobilization and at the same time, to apply efficient pressure over the sciatic nerve as it is "bowstringed" across the popliteal space (Fig. 4). The patient is

FIG. 2



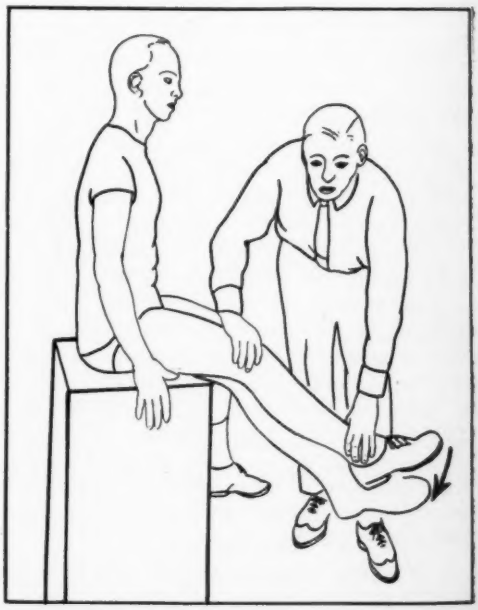
The knee is slowly, passively extended until the patient indicates when the pain is reproduced.

FIG. 1



After the desired position is selected, the patient is instructed to sit motionless throughout the test.

FIG. 3



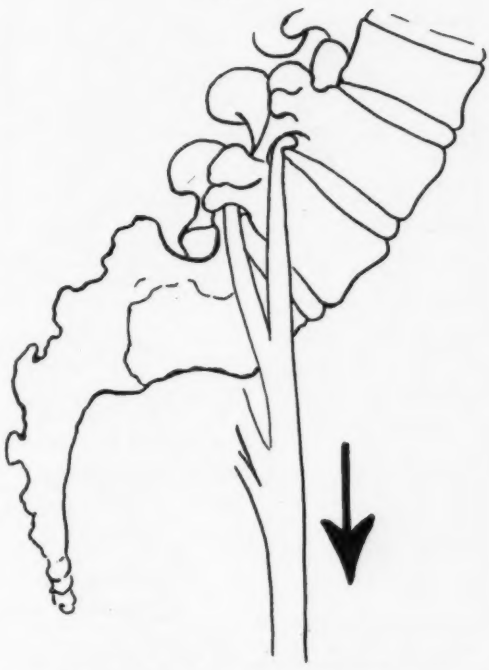
The knee is then passively flexed to a point just below the threshold of pain.

instructed to sit on a table, holding the back as straight as possible and sitting directly in line with no twist. He should brace himself with his hands. The patient is instructed not to move his back or any portion of his body (Fig. 1). The affected limb is extended passively at the knee until the patient states that the leg pain or a portion of his pain is reproduced (Fig. 2). The leg is lowered just below the point of pain (Fig. 3) and is held clasped between the knees of the examiner with the second and third fingers of both hands pressed upon the sciatic nerve in the popliteal space which has been "bowstringed" by this procedure. Pressure can be made directly over the tense "bowstring" sciatic nerve (Fig. 4). This causes some local discomfort, but this is much overshadowed by the severe reproduction of the patient's sciatic pain. This reproduction of pain may be the entire pain or any portion of the pain of which the patient complains. Pressure may be applied over the popliteal space with the leg fixed (Fig. 4) in the position of maximum pain (Fig. 2). The test differentiates the root compression syndrome from other causes of back and leg pain, and is also helpful in determining the severity of the root compression syndrome. The test is the earliest objective sign of nerve root pressure.

FIG. 4

With the leg locked between the examiner's knee at the sub-pain level, pressure is applied over the sciatic nerve in the popliteal space. In a positive case, pain is reproduced in the back or leg, or both.

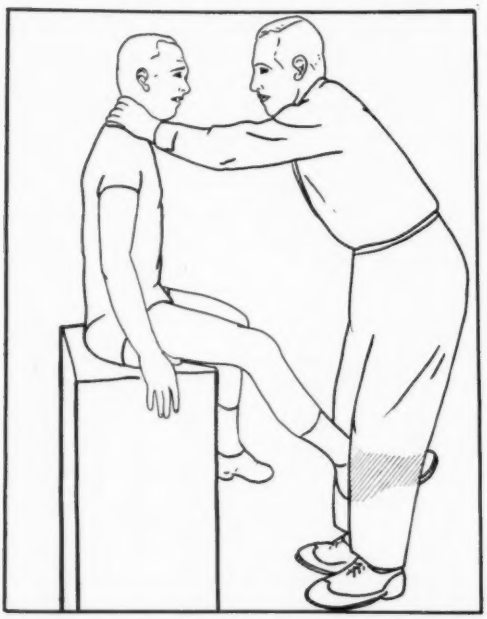
FIG. 5



Pressure over the sciatic nerve in the popliteal space causes motion and tension on the sciatic nerve. This tightens the nerve root at the point of the disk rupture, or other encroachment upon the nerve root.

The test may be performed on the contralateral leg, and if it reproduces pain on the painful side, it is suggestive that any herniated disk may be in the region of the crotch of the nerve rather than laterally where it is usually placed. In borderline cases the position may be altered to one of forward flexion of the head and trunk with dorsiflexion of the foot (Fig. 1, A); all of these motions are done prior to starting the test. The patient should again be instructed to maintain this attitude throughout the test. This latter position increases the tension of the nerve root and dura, thereby increasing the sensitivity of the test. Very occasionally the test will be positive only when the patient is placed on a hyperextended position prior to the test (Fig. 1, B). The mechanism of this would appear to be either further expulsion of disk material or pressure from the posterior structure such as the inter-

FIG. 6



With the nerve in this tightened position, a jugular compression test is more sensitive.

facet joint, which might be swollen, or from a cartilagenous plaque in spondylolisthesis. Most tests, however, that are positive in this position are also positive in the normal position or flexed position. A jugular compression test performed with the sciatic nerve in its position of maximum vulnerability is more likely to be positive as it is a more sensitive test (Fig. 6).

Interpretation

The principle of this test as described by Cram[3] is a production of tension on the tense "bowstringed" sciatic nerve, which tends to tighten it up in the region of its origin from the intervertebral rami and to cause motion at this site. If a rupture of a disk is present, it actually causes the nerve root to be pulled over the disk. This principle is applied in this new test by having the patient's carefully fixed position place the nerve on tension in a position of maximum vulnerability to motion, tension and pressure just below the threshold of pain. Pressure over the "bowstring" sciatic nerve in the popliteal space is the only motion that takes place during the test (Fig. 4). This pressure is transmitted as tension up the attenuated sciatic nerve to the intervertebral foramen (Fig. 5). Any encroachment on, or irritation of a nerve root will cause a reproduction of the patient's pain, all or in part. This reproduction of any of the patient's pain is a positive test and indicates nerve root pressure or irritation. The test will not be positive when there is referred sciatica resulting from irritation of one of the branches of the posterior ramus of the spinal nerve, as no motion occurs in the region of these nerve endings.

A positive test is the first sign of nerve root pressure, and is frequently positive long before any other signs can be demonstrated. Due to the selectivity of the test there are few false positives. It is felt that those positive tests eventually subsiding on conservative treatment were due to true nerve root pressure. The pressure had been due in part to edema in and around the nerve root. When this subsides the test may become negative and the patient improves. We feel these patients require longer and more persistent conservative treatment as they are more likely to require operation (Table 4). This is true even in those cases becoming negative very rapidly.

A straight-leg raising test with movement taking place at the back and hip will not make this distinction. The straight-leg raising test is usually positive in any conditions involving the supporting structures of the low back, such as simple myositis, muscle strain or other conditions sufficiently severe to stimulate the nerve endings of the posterior rami. Since these structures do not move in this new test, any pain must be the result of tension applied directly to the sciatic nerve.

Additional Uses of the Position and Test

Once the initial examination has been done, the patient may be tested for this sciatic tension test by having him sit in an office chair with his elbows resting on the arms. This is the most efficient way of following progress of conservative treatment, and one obtains more information from this than from a more formal follow-up examination of the patient which was done previously before the use of this test. As a result of the selective manner in which the patient's pain is reproduced, both physician and patient have complete confidence in the test as a means of following the progress of treatment.

TABLE 1

	Number of Cases		Percentage
Responded to treatment	138		76
Required operation	44		24
Pathologic changes at operation (2 interspaces explored and spine fused)			
Definite disk disease	38		86
No disk disease (all 6, 100%, had negative sciatic tension test)	6		13
Diagnosed "unstable back"	5		
had positive straight-leg raising test		3	
had negative straight-leg raising test		2	
Spondylolysis (had negative straight-leg raising test)	1		

TABLE 2

	Number of Cases		Percentage
Definite involvement of disk, nerve root pressure	38		
Degenerated disk with spur formation		8	
Bulging disk		5	
Ruptured disk		25	
Extruded into canal		5	
Positive sciatic tension test (4 of these cases had negative straight-leg raising tests, 10%)	37		97
Negative sciatic tension test (An old degenerated disk with spur formation and dense adhesions about the nerve root) (Fig. 7).	1		2.6

Malingerers, or patients exaggerating their symptoms, may be recognized by this test. After going through the formality of the test up to the point where the patient is asked to tell when his pain is reproduced, the examiner has at this point his fingers over the sciatic nerve and his thumbs over the region of the patella (Fig. 4). After very expectantly asking the patient whether or not the next maneuver will reproduce the pain of which he complains, one reverses the procedure and does not press on the sciatic nerve, but instead, presses very firmly over the patella. In some cases the patient will state that this reproduces his entire pain; if he does so, it is obvious to the examiner that there is no anatomic mechanism whereby pressure over the patella, or on an otherwise immobilized leg, could cause any reproduction of back or leg pain. This would certainly indicate that the patient is malingering or exaggerating the facts considerably further than the examiner is stretching his sciatic nerve.

In patients who have questionable areas of numbness, the patient is placed with the leg just below the threshold of pain, or actually into the area of pain. An assistant then holds the foot, or props it in this position on a chair and leaves the patient for five to ten minutes, depending upon his tolerance of the pain. On return, the examiner will find that the questionable areas of numbness will be more well delineated as a result of holding the nerve in its position of maximum vulnerability to pressure, making more definite the symptoms of pressure on the nerve root. It is not necessary to have pressure maintained on the sciatic nerve in the popliteal space, but merely to keep the knee sufficiently extended to put it on tension.

Over a seven months period we saw 182 patients with low back pain and/or sciatica. The shortest follow-up on these patients was 6 months. All patients were initially treated conservatively[4] (Table 1).

It will be noted from this table that of the 6 patients with no disease of the disk, all had negative sciatic tension tests. Of the 38 cases with definite disk pathologic changes of the disk as shown at operation, the following facts were recorded (Table 2).

In a previous report,[4] of 79 cases of nerve root pressure demonstrated at operation, only 71 or 90 per cent had a positive straight-leg raising test, so the test is more accurate in our hands than the simple straight-leg raising. The one patient who had disk disease and nerve root pressure without a positive sciatic tension test was the case of a 52 year old woman with an 8 year history of back pain. For the past 2 years she had had some pain in her leg, going as far as her knee. She failed to respond to conservative treatment and after 6 to 8 months, in view of her inability to live with her discomfort, her back was explored. Preoperative x-ray studies had shown massive spur formation at the fourth lumbar interspace. At operation the nerve foot was found to be bound down tightly with scar tissue and pressed up in a ribbon-like fashion over the spur formation at the fourth lumbar inter-

TABLE 3

	Number of Cases	Percentage
Negative sciatic tension test (20 had positive straight-leg raising tests, 13%)	127	93
Positive sciatic tension test (Positive straight-leg raising test also present)	11	8

TABLE 4

	Number of Cases	*Percentage*
Negative tests	134	
Required operation	7	5
Responded to treatment	127	95
Positive tests	48	
Required operation	37	75
Responded to treatment	11	25
	182	

space (Fig. 7). There was also present some recent rupture of degenerative material from between the spurs. The patient obtained a good result and my explanation for the reason that she did not have a positive test was the fact that it was an old case and the nerve roots were so bound down with adhesions that it was very difficult to move the nerve roots at operation and would be more difficult to move them with any tension from below.

Of the 182 cases treated conservatively, 138 responded sufficiently to avoid operation (Table 3).

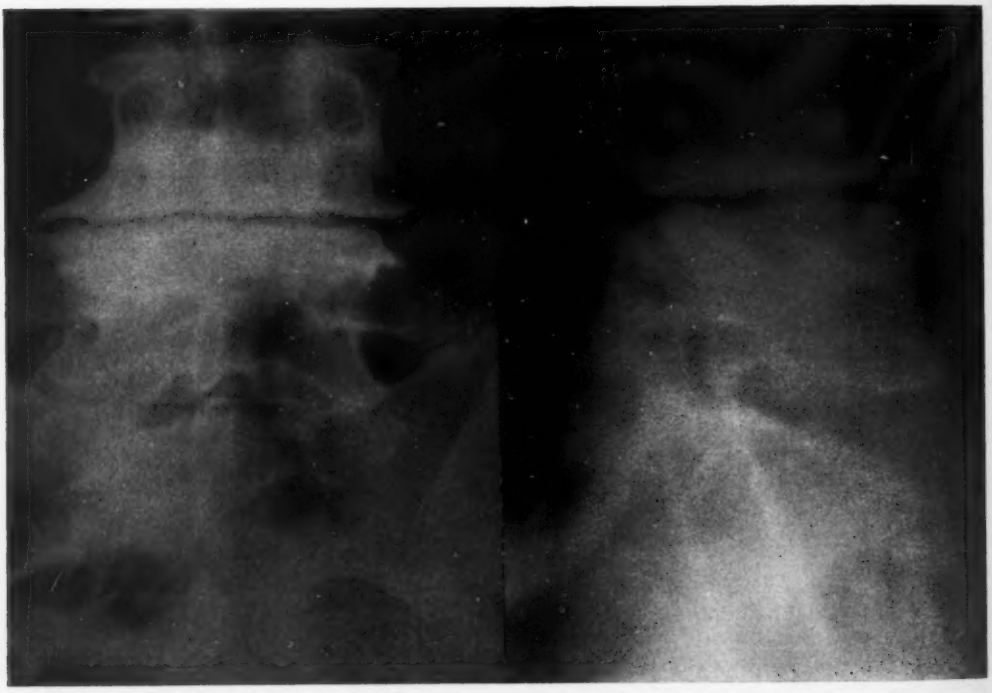
It will be seen that there were 11 instances of positive sciatic tension tests. We felt that these responded to conservative treatment because of the allowance of time for subsidence of edema around the nerve root. These may eventually come to operation.

Of the 182 consecutive cases, a breakdown of the results of those requiring operation after all were given a trial of conservative treatment, is as shown in table 4.

From this it can be seen that a patient with a positive test has a 75 per cent chance of requiring operation, or a patient with a negative test has a 95 per cent chance of not needing an operation. We feel that this is an important distinction to make early in the treatment of all back conditions from a prognostic standpoint, for even in cases of acute back strain, if there is a positive test, one knows definitely that there is some nerve root pressure. This patient certainly has to be treated longer and more thoroughly with a conservative regimen if he is to avoid the possibility of further rupture of disk material.

Table 5 shows a breakdown of the proportion of leg and back pain of the 138 cases responding to conservative treatment.

FIG. 7



X-ray study in the one case that had nerve root pressure, but a negative sciatic tension test.

TABLE 5

	Number of Cases
Negative "bowstring" and negative leg-raising tests	107
Back and leg pain	16
Back pain only	88
Leg pain only	3
Negative "bowstring" and positive leg-raising tests	20
Leg and back pain	12
Back pain only	8
Positive "bowstring" and positive leg-raising tests	11
Leg and back pain	8
Back pain only	2
Leg pain only	1

Conclusions

A new very sensitive test for differentiating the pain of nerve root pressure from pain produced by other mechanisms in the low back has been presented.

In our hands this test has been the best single method of diagnosing nerve root pressure.

This test is a very accurate guide as to whether or not surgical intervention might eventually be required.

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Discussion (Abstract)

Dr. Bruce M. Cameron, Houston, Tex. Dr. Deyerle has presented us with an excellent paper. I have not had as much clinical experience with this test as he has, but since reading his paper, I have used it and have asked several of my neurosurgical colleagues to use it in the differentiation of low back pain. They have stated that the test has been positive in a high percentage of cases in which the patients have had to be operated upon and which were shown to have a herniated disk or some other cause for nerve root pressure. It was especially helpful in the diagnosis of functional back pain.

We were quite interested to find out for ourselves that there was a sound anatomic basis for this test, and we tried this out, as described by Dr. Deyerle, in the laboratory on three dissected specimens. We found to our surprise that not only was there a tug at the nerve roots with the test but there was an actual excursion produced with this test.

We feel that the diagnosis of a herniated disk requiring operation, or any other disease of the nerve root needing surgical attack depends not upon just one single test such as this, and we are sure Dr. Deyerle feels the same way. It depends upon a composite of a careful history, physical, x-ray examination, conservative therapy, observation of the patient, and finally that indescribable thing called clinical judgment and experience, and proper selection of the patient or the candidate.

However, we do believe that this test has a sound anatomic basis and is a valuable adjunct in the diagnosis of low back pain.

Dr. Deyerle (Closing). I did not mean to infer that this test is used in lieu of a history and physical examination. It is an adjunct. I will say that once one has done the initial "workup" and has determined what one is going to do (and in our case, we treat them all conservatively initially) one can follow treatment by having the patient simply sit in a chair and go through this test. Both you and the patient have more confidence that you know more about his progress than we previously ascertained by more detailed disrobing and many manipulations. The patient gets very possessive. He says that is his pain, and when you can reproduce his pain, he knows it and you know it.

The test does not replace the physical examination or history, but it is an excellent adjunct, and is one of the simplest ways I know of determining the progress of treatment.

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Squamous Cell Carcinoma of the Anus: A Case Report*

R. SAM MOSLEY, M.D., *Coral Gables, Fla.*

This lesion makes up a small proportion of carcinomas of the gastrointestinal tract. However, it is amenable to radical surgical attack.

ALTHOUGH SQUAMOUS CELL CARCINOMA OF THE ANUS is a relatively rare disease, there have been many papers written on this interesting subject during recent years. This lesion is also frequently referred to as epidermoid carcinoma of the anus. Two types are generally recognized, the basocellular type and the spindle-celled epithelial type. The former represents less than 2 per cent of the total. It is the purpose of this paper to give a brief review of the literature, followed by a case report. To emphasize the rarity of this disease, my case is the first so diagnosed in 39,624 adult admissions of the Doctor's Hospital, Coral Gables, Florida. This case is one of two that has come under my supervision.

Most authors report that this condition occurs slightly more often in females than males. In common with other malignancies the patient's age is usually between 55 and 60. There seems to be no relationship to race or geography.

The anal canal is lined with squamous epithelium which is continuous with the mucous membrane of the rectum above and the true perianal skin below. The dentate line is the point at which the stratified epithelium of the anal canal changes to the simple columnar epithelium of the digestive tract. There is a transitional type of epithelial cell at the cephalad margin of the canal. Squamous cell neoplasms usually arise from the epithelium of the anus and then invade the rectum by contiguous growth across the dentate line. It is very rare that the squamous cell carcinoma has been known to arise above the dentate line and it is thought that these few cases may have been due to residual embryonic cells.

*Read before the Section on Proctology, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

Review of the Literature

Most observers are in remarkable agreement on the ratio of squamous cell carcinoma of the anus to adenocarcinoma of the rectum. The foreign literature usually states that epidermoid carcinomas represent from 1 to 6 per cent of the total. The Mayo Clinic[1] puts the figure at around 1 per cent. Cattell[2] found them to represent 1.7 per cent of the total at the Lahey Clinic. Hayden[3] found that they represent about 1 per cent of all malignancies of the colon and rectum. Bacon[4] gives a figure of 6 per cent. Grinnell,[5] in a study made at the Presbyterian Hospital of New York City, noted that anal tumors comprised 1.8 per cent of the combined anal and intestinal tumors and 4 per cent of the combined anal and rectal lesions. This is astoundingly similar to ratios obtained at the Doctor's Hospital of Coral Gables, Florida. My studies there show that the anal tumors represent 1.6 per cent of the combined anal and large intestinal tumors and 3.2 per cent of the combined anal and rectal lesions. The etiology of anal tumors is as conjectural as malignant tumors found elsewhere in the body. Although some authorities think that chronic irritation plays a part in their creation, this theory has its opponents. Epidermoid carcinomas have been known to become superimposed on benign anal conditions such as hemorrhoids, fissures and fistulas, but it is my opinion that these were simply coincidental. Rosser[6] in a study of 13 anal cancers was able to establish the fact that 12 of these were preceded by benign anal disease. Cattell[2] believes that this benign disease plays an etiological part in the development of malignancy. Lyons and Garlock[7] of Mount Sinai Hospital, New York City, noted that operations for anal conditions, such as hemorrhoids,

fissures or abscesses, immediately preceded the diagnosis of squamous cell carcinoma in about 20 per cent of cases, indicating the frequency of error in diagnosis. Acute abscesses were associated in 10 per cent of the cases.

Although this tumor is more invasive locally, it is slower growing than rectal adenocarcinomas. Extension is usually by contiguity. It may spread superficially along the perineum to the scrotum or vulva, or deeply into the anal sphincter muscles, prostate and rectovaginal septum. Spread through the lymphatic pathways and very seldom through the blood stream may occur. Metastases are less common and less widespread than in adenocarcinoma of the rectum. The liver is practically never involved. The lymphatic spread may go anteriorly and involve the inguinal nodes or it may go posteriorly and involve the nodes in that region. Cephalic spread is less frequent. Practically all of these tumors invade the sphincter muscles and many spread upward into the rectum, usually outside of the lumen. Grinnell's[5] series showed only 8.2 per cent metastasis to the inguinal lymph nodes. He found a 28 per cent cephalic spread from anal carcinoma as compared to a 42.2 per cent spread from adenocarcinoma of the rectum. He found the prostate involved in only 3 of his cases.

Due to the lack of early symptoms in the growth of this tumor, diagnosis is frequently dangerously delayed. The patient is often aware of a growth or some presumably benign lesion in the anal region long before he seeks medical advice. He is not likely to seek a diagnosis until bleeding and pain become prominent symptoms. Pain is likely to become excruciating and tenesmus pronounced as the tumor invades the sphincter muscles. In the Mount Sinai series,[7] symptoms existed from 1 month to 2 years before medical opinion was sought and, in the Presbyterian Hospital series,[5] the average duration of symptoms was 7.8 months. The final diagnosis is made by the pathologist from a biopsied specimen. Recommended therapy has undergone considerable change during the past 15 years.

Prior to 1940, irradiation of these lesions was quite popular, but since that time radical extirpation of the rectum and anus has become more popular. In a few of the larger medical centers treatment continues to combine the two. The general opinion now favors surgical excision for the large lesions, reserving irradiation for the small localized external lesion at the anal verge. Cattell and Williams[2] believe that irradiation should be used only on the inoperable and recurrent lesions. Judd and Detar[1] of the Mayo Clinic believe that local excision should never be employed in the treatment of this tumor. Grinnell[5] states that early radical surgery can be expected to improve the cure rate in the future. Several factors influenced the transition from irradiation to surgery: the 5 year survival rate following irradiation was not too impressive; patients undergoing irradiation had severe pain and discomfort; anal stricture and fecal incontinence occurred frequently; and, most observers had considerable doubt as to whether irradiation can destroy cancer cells in metastatic lymph nodes such as the perirectal and the mesocolic nodes which are not easily accessible. It now seems to be generally accepted that the inguinal nodes need not be resected unless there is definite evidence of metastasis in that region. Earlier these were routinely removed. Some authorities recommend that these should be irradiated after radical removal of the primary lesion.

Before concluding this paper I wish to incorporate a case report.

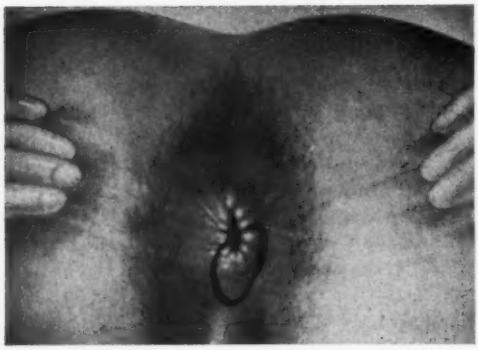
Case Report

H. O., a 72 year old white man, consulted me in January 1954, for a sore swelling between his anus and scrotum. This swelling had not concerned him until 6 months previously when it began to get increasingly sore. He was aware of the swelling and said that a doctor had called his attention to it as far back as 1947. He had subsequently seen other doctors for other ailments but only one of them had made a note of the swelling. This doctor referred the patient to me. The patient's only other current complaint was a greater difficulty in urinating. He denied any pain with bowel movements. He had seen no blood in his urine or feces and his bowels acted fairly normally. He noticed a slight protrusion from the anus at one time.

His past history included an appendectomy in 1920, and a suspected duodenal ulcer which healed some 5 months previously according to his doctor. His weight has remained static around 180 pounds. He had been having nocturia for several years. He denied the use of alcohol or sedatives of any kind.

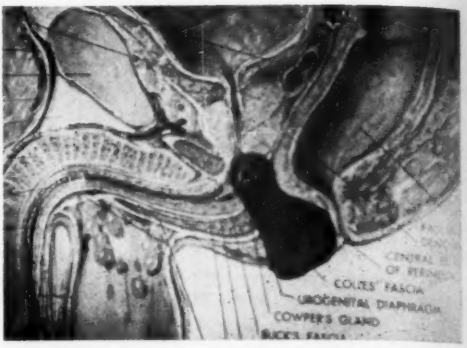
Physical examination revealed a well-developed white man weighing 180 pounds, with normal temperature, pulse and respiration. The blood pressure was normal. Perianal inspection revealed a hard

FIG. 1



Encircled area shows location of tumor. The elevated skin felt hard and gristly.

FIG. 2



Diagrammatic sagittal section of pelvis showing extent of tumor growth found at the time of operation. Note invasion of prostate and membranous urethra.

gristle-like growth immediately anterior to the anus (Fig. 1). This produced elevation of the skin in that area when the patient's thighs were acutely flexed. This growth extended one and a half inches up the anterior rectal wall external to the lumen and anteriorly about one inch. It extended farther to the right than to the left. No connection between the growth and the genitourinary tract could be determined at this time. The anoscopic examination revealed moderate combined hemorrhoids in the right anterior quadrant. There were large internal hemorrhoids in the right posterior and left lateral quadrants. The sigmoidoscope was passed to the rectosigmoid juncture and no disease was found. The prostate was examined and was found to be small and soft. Secretions from the prostate revealed moderate white blood cells with a few clumps.

On January 25, at the Doctor's Hospital, Coral Gables, Florida, a biopsy was made of the tumor mass. The pathologist's report was as follows: The specimen consists of a triangular segment of firm tissue measuring 2.2 cm. On section it is uniform and fleshy in consistency. There are irregularly invading, infiltrating cords and nests of atypical squamous epithelial cells. The nuclei have slight to moderate variations in size and shape with occasional mitoses. Aberrant keratinization is light. A heavy poly infiltration is present. *Diagnosis:* Primary squamous cell carcinoma of the anus, grade I.

At this point the question arose as to the correct way of treating this known carcinoma. Three choices were considered: (1) a local excision of the entire mass, making this a complete perineal procedure; (2) irradiation; (3) combined abdominal perineal resection. Local excision lessened the chance of removing all of the cancer cells. The tumor had infiltrated into the sphincter fibers and it would have been necessary to remove all of the anal sphincter in the anterior quadrants. This would have left us a very unhappy patient with fecal incontinence. Radiation therapy was not considered very seriously because the amount of radiation needed would have been so great that the adjacent soft tissues would have been considerably damaged causing the patient excruciating pain plus considerable scarring of the anal canal with subsequent stenosis of the canal.

On January 30, 1954, the combined abdominal perineal operation was performed. The sigmoid was severed at the junction of the upper two-thirds and the lower one-third. The proximal end was brought into the abdominal wound in the mid-line two inches below the umbilicus. After freeing the rectum and reconstructing the pelvic floor the abdomen was closed in layers. The rectum was removed from below and great difficulty was encountered during this portion of the operation. The tumor mass was found to be adherent to the bulbous portion of the urethra and the prostate (Fig. 2).

A portion of the prostate and the urethra had to be excised to remove the tumor mass. The perineal wound was packed with gauze and the posterior two-thirds sutured with black silk.

The excised specimen was sent to the pathologist for evaluation. He gave the following report: The specimen consists of 25 cm. of rectum and anus. At one end there is a fibrous type tumor mass measuring 6.5 by 4 cm. The appearance on section is pinkish in color and considerably fibrous in consistency. It appears to replace a part of the anus. There are no adjacent involved lymph nodes. The tumor is made up of irregularly invading cords of squamous epithelium cells (Figs. 3 and 4). The nuclei have slight variations in size and shape. Aberrant keratinization is light. Mitoses are occasional. There is intense surrounding mixed inflammatory infiltration and fibrosis. Necrosis is present. Invasion of the voluntary muscle is noted. *Diagnosis:* Primary squamous cell carcinoma of the anus, grade I-II.

No palpable inguinal lymph nodes were found and consequently no excision was done in the groin area. A retention Foley catheter was placed in the bladder and this was connected for continuous drainage into a bottle.

On the tenth postoperative day a plastic repair of the colostomy was performed with the removal of all tissues protruding beyond the abdominal skin margin. The colostomy had started to function well by

the fifth postoperative day. The patient was sufficiently strong and recovered enough to go home on his twenty-ninth postoperative day. During the postoperative convalescence the patient's progress was hampered by pulmonary congestion attributed to small multiple pulmonary emboli. There were several episodes of auricular fibrillation.

Although the abdominal wound had completely healed by the thirteenth day, the perineal wound continued to keep a small draining sinus. This was found to extend down from the posterior aspect of the prostatic urethra. For approximately three months following the abdominoperineal resection the patient was reasonably comfortable and ambulatory.

He was returned to the hospital in May for study and observation, and the remainder of the prostate was removed on June 7, 1954. Additional tumor tissue was found at that time. This was removed along with the fistulous tract. Again the pathologist reported squamous cell carcinoma. Following this operation the perineal wound remained open with a mucopurulent discharge, frequently bloody. It became apparent that more of the tumor remained around the neck of the bladder and adjacent tissues. Hematuria became a frequent occurrence.

Extensive x-ray irradiation was begun in July, but as far as could be determined this did not alter the course of the tumor growth.

The perineal wound continued to slough and drain despite all treatment. Intensive supportive treatment prolonged the patient's life but he expired in January 1955, from extreme cachexia. An autopsy was not permitted.

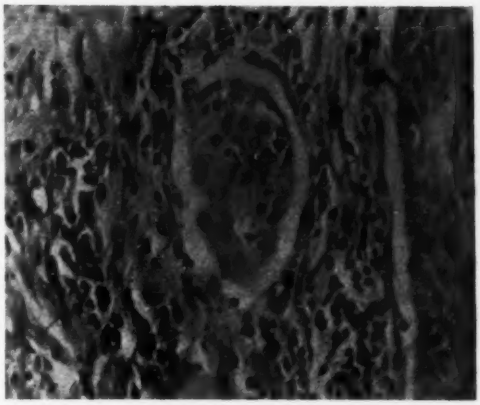
Summary

From a study of the recent literature on squamous cell carcinoma of the anus, which was excited by an interesting case of my own, I think we can briefly summarize the subject as follows: This is an extremely rare tumor, representing less than 2 per cent of the tumors of the intestinal tract. It is insidious in onset and, as in the case reported, may be asymptomatic for several years. All tumor masses in the anal area should be suspected and biopsied. Extension is usually by contiguity, but there may be spread through the lymphatic pathways and rarely through the blood stream. Less than 10 per cent of the reported cases had spread to the inguinal lymph nodes. Whereas irradiation used to have a prominent place in the treatment of these lesions, most of the surgeons in the larger medical centers now feel that early radical surgery is better. Irradiation may cause the loss of valuable time in the treatment of this tumor. The combined abdominoperineal resection is considered the operation of choice and only rarely is local excision indicated. Routine excision of the inguinal glands is of doubtful value. Although the present five year survival rate for this tumor compares favorably with that of adenocarcinoma of the rectum, this should be improved with a greater use of radical surgery.

FIG. 3

Low power section of tumor. Note irregularly invading, infiltrating cords and nests of atypical squamous epithelial cells.

FIG. 4



Section of tumor, high power.

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Discussion (Abstract)

Dr. Patrick H. Hanley, New Orleans, La. I thoroughly enjoyed Dr. Mosley's comprehensive review of this subject and presentation of a case. Dr. Edgar Boling asked that I discuss Dr. Mosley's paper for Dr. R. Leeves McCarty, who was unable to attend the meeting because of family illness.

During the last 12 years we encountered 41 cases of epidermoid carcinoma at Charity Hospital in New Orleans and at the Ochsner Clinic. I would like to show a few slides of cases selected from our experience with this interesting and rare proctologic problem.

This slide shows a typical lesion of an epidermoid carcinoma of the anus. As brought out by Dr. Mosley, it is usually located in the anorectal junction, and although the ulceration itself is small, you can see that its upward extension into the rectum is really submucosal for a distance of 7 or 8 cm. The ulcer itself is an innocent looking lesion, only about 1 by 1.5 cm. This patient had perirectal lymph node involvement.

As Dr. Mosley also brought out, sometimes these epidermoid carcinomas spread superficially over the cutaneous surface instead of deeply, as shown in this slide where the lesion extends over to the vulva and anal area.

This slide shows a typical severe ulcerative type of carcinoma that infiltrates into the anal mechanism.

The next slide is of interest from the standpoint of etiology. We believe that chronic inflammatory disease plays a definite part in the etiology of epidermoid carcinoma. We had epidermoid carcinoma develop in 5 patients who had had chronic inflammatory disease for 20 to 23 years. This patient had a fistula-in-ano. Biopsy showed a low grade epidermoid carcinoma. I might add that all epidermoid carcinomas developing after long-standing inflammatory processes are of low grade. In these low grade epidermoid carcinomas, even though they are extensive, the condition is not hopeless.

We do not consider local recurrence of epidermoid carcinoma as necessarily hopeless. If we think there is any possibility of extirpating a locally recurrent lesion, we attempt to do so. This slide is of a patient who had a recurrence anteriorly in the perineal body, so we removed the perineum, vagina and coccyx. She has a prolapse, but she has remained well without recurrence for a period of two years. The next slide, the same patient, shows the location of the urethra while the patient is not straining.

This slide is shown to stress again the importance of chronic inflammation in the etiology of epidermoid carcinoma. This patient had extensive hidrosadenitis for 20 years. Following excision a primary split thickness skin graft was applied. (Slide) The patient failed to return to the clinic for 7 years, and at that time he had an epidermoid carcinoma right near the anus, which was treated by combined abdominoperineal resection. The large perineal wound shown in this slide was photographed about two weeks postoperatively. The next slide was made about five weeks postoperatively; in the lower part of the wound can be seen a few white spots. The little white spots on the granulating surface of the perineal wound resemble healthy epithelization of a pinch skin graft. However, biopsy proved this to be a local recurrent growth. I really believe that local recurrence in epidermoid carcinoma is due chiefly to local transplantation at the time of operation. We do not believe that this is a hopeless situation for radical excision of these local recurrent lesions can result in cure, especially if they are due to transplants.

The next slide shows a small epidermoid carcinoma that appears to be insignificant (3 by 4 mm.). These are the cases that present a problem in treatment. We consider combined abdominoperineal resection to be the treatment of choice in such cases. This is the type of case in which some surgeons might compromise in treatment. The small size of this type of cancer may be misleading, as they are known to be dangerous. We had a patient with a carcinoma only 4 mm. in size but he had metastasis in the intermediate nodes. Dixon reported a case of epidermoid carcinoma of the rectum in which the decision to perform a biopsy of a little pea-sized carcinoma actually cured the local lesion, but after the abdominoperineal resection, the patient was found to have metastasis. Therefore, even in small epidermoid lesions, the radical procedure is indicated.

The Use of Soluble Nonabsorbable Opaque Media in the Examination of the Gastrointestinal Tract in Children*

LAWRENCE A. DAVIS, M.D.,† *Louisville, Ky.*

The author applies the use of radiopaque substances usually used in urography to the demonstration, under special circumstances, of gastrointestinal lesions in infants.

BARIUM SULFATE IS A USEFUL AND CHEAP RADIOPAQUE medium in the examination of the gastrointestinal tract, but it has certain disadvantages and drawbacks which reduce its usefulness. The tendency to inspissate causes difficulty in examining obstructed areas, particularly of the large bowel. The fairly thick nature and particulate character of barium suspensions often makes it unsuitable for delineating minute fistulous tracts. For these reasons a water-soluble, nonabsorbable medium for examining the gastrointestinal tract was sought.

Suitable media were found in the group currently in use in excretory pyelography, Urokon and Hypaque. These materials are true solutions, nonparticulate, of low viscosity and nontoxic.

The toxicology of both Urokon and Hypaque has been investigated by our Department of Pharmacology, and both have been found safe for oral administration in humans. In a controlled group of adults, only about 2 per cent of an ingested dose of Urokon was recovered from the urine. Thus, 98 per cent of the material was excreted through the bowel.

Several obvious drawbacks present themselves: (1) the materials are tremendously expensive as compared to barium; (2) they have a very bitter taste and (3) the osmolarity of these solutions in full strength (70 per cent) makes them effective saline-type cathartics.

Because of these factors, their use in adults has been limited to very special cases.

In infants, however, we have found them most useful and practical. In our routine gastrointestinal examination in this age group, we administer the opaque through an indwelling esophageal tube, thus eliminating the factor of bad taste. A 25 cc. ampule of 70 per cent Urokon can be diluted with 50 cc. of water, thus giving 75 cc. of a 23 per cent opaque medium. This is more than enough for the average infant and is quite opaque for both fluoroscopic and radiographic purposes. In effect, we usually find a 25 cc. ampule of a 50 per cent solution diluted to a total volume

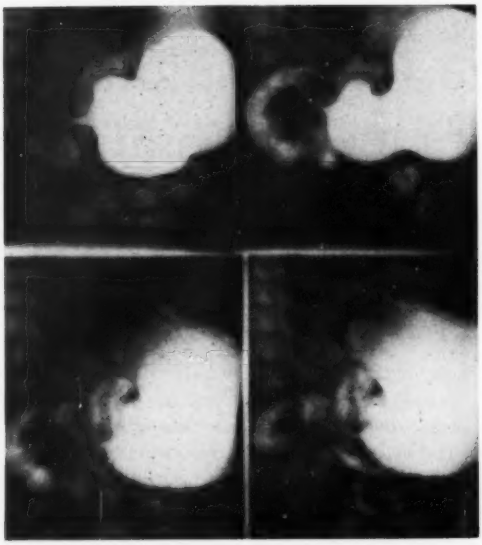
FIG. 1

Colon visualized 1 and 1/2 hours after oral administration of opaque.

*Read before the Section on Radiology, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

†From the Children's Hospital, and the University of Louisville School of Medicine, Louisville, Ky.

FIG. 2



Pyloric stenosis demonstrating the "string sign" as well as impression upon the base of the duodenal bulb by the hypertrophied muscle.

of 50 cc. quite adequate. In our series, so far, we have had no complaints of diarrhea. The osmotic effect of these opaque media, however, is readily apparent since its passage through the gastrointestinal tract is very rapid (Fig. 1). The additional cost of the gastrointestinal examination which is equal to that of an intravenous pyelogram should be no deterrent if the opaque medium proves advantageous.

Studies

We have used these substances in 42 patients, equally divided between Urokon and Hypaque. No radiographic or clinical differences between the drugs have appeared.

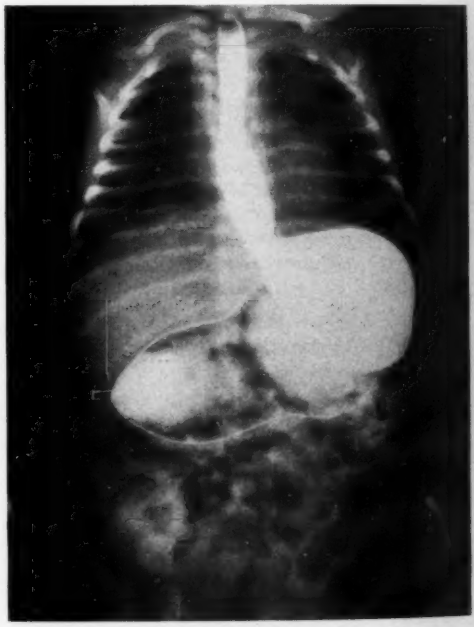
In the esophagus, the thinness and low viscosity of the solutions should make them ideal for finding small tracheo-esophageal fistulas. So far, we have not had the opportunity of detecting one. In the ordinary tracheo-esophageal fistula with atresia, we use 2 to 3 cc. of a medium, injected into a tube whose tip is in the blind sac. A single, lateral film is sufficient for diagnosis. We have dispensed entirely with the oily opaque materials.

The water soluble opaque substances make the detection of pyloric stenosis an easy matter. We have had eight cases during the last year (Fig. 2). In no instance did it take more than 10 minutes to outline the narrowed antral segment, and usually it filled with passage of the opaque medium into the bulb within two minutes.

Detection of small gastric esophageal hernias and gastroesophageal incompetency is facilitated by the better mucosal outlining qualities of these materials (Fig. 3).

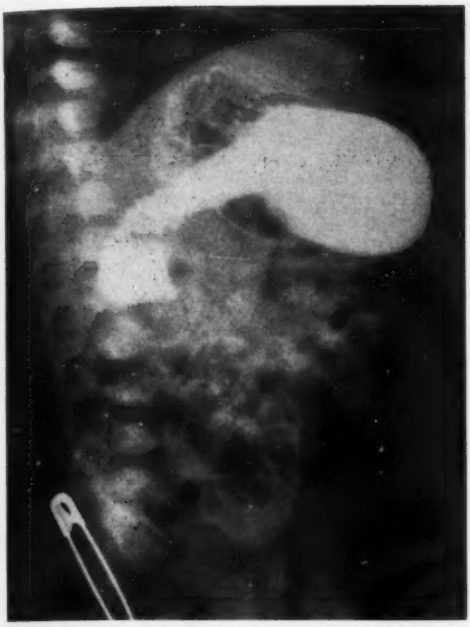
In general, most surgeons and many radiologists are hesitant in administering barium suspensions to newborn infants suspected of having atresias or stenoses of the small intestine. Nevertheless, in many patients, air is not the best contrast media, and the possibility of low ileal atresia can only be ruled out with great difficulty. By the use of the media under discussion, in the more obvious cases the site of obstruction can be quite exactly localized, and this has proved most helpful to the surgeons (Fig. 4). Since the materials are water soluble there is no danger of inspissation, nor is there any danger if peritoneal spillage should occur. The rapid transit of the substance also proves advantageous. In a recent case, a newborn infant had passed no meconium for 24 hours following birth, and

FIG. 3



Gastroesophageal incompetency with marked regurgitation.

FIG. 4



Duodenal stenosis with demonstration of the occluded area in the transverse duodenum.

though scout films were normal, a partial low, ileal stenosis was suspected. Administration of 50 cc. of 25 per cent Hypaque into the stomach was followed by serial films, and within one hour the small bowel was outlined with no evidence of obstruction. Subsequently, the infant passed a stool and no abnormality appeared later.

In the small bowel many obstructions of the duodenal area have been outlined. These include the classical atresias of the newborn as well as several cases of stenosis. A recent patient proved very interesting. An 11 month old girl, weighing 19 pounds, was admitted because of recurrent cyclic vomiting since birth. At times food taken three days previously would be regurgitated. The mother also had noted abdominal peristaltic waves. Fifty cc. of 25 per cent Hypaque passed immediately through a patulous pyloric canal into a tremendously dilated duodenal loop. Food particles were noted as negative shadows throughout. At laparotomy a high grade obstruction in the region of the duodenojejunal junction was discovered and by-passed by an enterostomy. It is interesting that within 18

FIG. 5

Aganglionic megacolon. Arrow points to involved segment. Note hypertrophied muscle folds proximal to obstruction.

FIG. 6

Cystogram showing reflux visualization through a cloaca of the vagina and uterine cavity.

hours the colon was well outlined and aided in discarding, without further study, the possibility of a malrotation.

In infants, 50 or 75 cc. is sufficient to outline the colon by enema. Injection by a 100 cc. syringe is convenient and easy. There is no fear of completing a partial intestinal obstruction in megacolon, and we routinely use the materials if megacolon is suspected in an infant. In one patient the hypertrophic mucosa proximal to the obstructed site was well seen as was the aganglionic segment (Fig. 5).

Outside the gastrointestinal tract we have used these materials for delineating the lower genitourinary tract in attempting to determine the sex of an infant. Figure 6 shows the cervix and uterine canal visualized following injection of the common cloaca.

Conclusion

The water soluble, nonabsorbable radiopaque media used in urological roentgenography are valuable in examining the gastrointestinal tract of infants. The fact that they are of low viscosity, do not inspissate, and are nontoxic makes them superior to the ordinary barium mixtures in many cases.

Discussion (Abstract)

Dr. Robert D. Moreton, Fort Worth, Tex. Dr. Davis has introduced the use of a group of opaque media, with which we are familiar, to a field entirely separate from their intended use.

Certainly, the fact that they are true solutions and, if absorbed or injected into the body cavities, are relatively nontoxic is very desirable. A more marked advantage would seem to be the low viscosity of these solutions in demonstrating very small pathological conditions which a more viscid one would not outline.

The main objection to the oral use of these substances is the very bitter taste and necessity of using a tube. Certainly, for the patients in the hospital, already having a tube in place, this would not be unsatisfactory and these media might be those of choice.

I would like to ask Dr. Davis if he thinks this method should be considered for a routine examination, and if he would expect to encounter any problems in iodine sensitivity. In the occasional selected patient the cost would be of no consideration but would the comparative cost be too great to consider for a routine if masking solutions were satisfactory? Would not the irritability which causes the diarrhea probably change the small bowel pattern in certain conditions?

I wish to thank Dr. Davis for the presentation and congratulate him on this fine work which may be found to open many new answers in our efficiency in gastrointestinal examinations.

Dr. Peter E. Russo, Oklahoma City, Okla. Dr. Davis, would you please repeat the dilution and amounts you use for the Urokon enema?

Dr. Davis (Closing). To answer the questions Dr. Moreton proposed, let me say that we routinely intubate all our children, whether inpatients or outpatients, below the age of three. We do not use the bottle and nipple as many institutions do. The water soluble opaque media are not used routinely in general, but are used following the administration of barium when some abnormality is present, or initially, when we strongly suspect an abnormality.

The cost at the present time for this examination would be similar to the additional cost for the medium in an intravenous pyelogram. In the indicated case that cost should not make any difference. We have no history or knowledge of iodine sensitivity being created by this material in oral administration, or have we any evidence of a rash or any of the other reactions following oral administration.

In answer to Dr. Russo's question,—we use the same dilution in the infant's colon as we do in the stomach, 25 per cent. Generally, we find that one 25 or 30 cc. ampule of a 50 per cent solution diluted with an equal amount of water up to 50 or 60 cc. is sufficient. Occasionally we have to double this proportion.

A Plan for the Conversion of a Tuberculosis Hospital to an Intermediate Facility for the Care of the Long-Term Case: The Importance of Such A Facility in Community Planning for the Medical Care of the Chronically Ill*

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Richmond, Va.

This is a very important paper in its description of a means of meeting a growing problem in every community. The problem is that of chronic illness, more often in the aged, but actually in all age groups. A solution is offered to provide hospital care beyond the acute phase of the illness, to provide rehabilitation and at a lesser cost to the taxpayer than maintaining a bed in the expensive environment of a general hospital. A few communities are facing this problem, many more will need to in coming years.

THE MECHANICS OF CONVERTING A TUBERCULOSIS HOSPITAL or sanatorium to an intermediate hospital facility for the care of long-term illness is a relatively simple and economical procedure. Particularly is this true if the transition develops in an orderly and well-planned manner. The mere process of physical conversion however, is relatively unimportant in comparison with the integration of such a hospital facility into the established medical service facilities of the community. In order to obtain maximum use of the facility and to achieve the economy that is desired, it is essential that integration be accomplished. In many parts of the United States, well-constructed tuberculosis facilities are being closed. In some areas they have been assigned to other governmental use and in others they have been completely abandoned. In many cases the simple process of conversion can turn these buildings into much-needed facilities for the care of long-term patients.

As we describe the transition of such a facility in Richmond, we believe that it would be best to present it in its setting as an actual part of a planned community chronic disease program. We will attempt to demonstrate the advantages of converting such a facility on a gradual basis. In Richmond, beds for the care of chronic disease were opened at the same rate that beds became available through the orderly discharge of tuberculosis patients. This process permitted the staff to adjust gradually to the transition. As we stated in our opening words, we believe that care of the chronically ill patient should be well thought out and that the community should have a well-organized plan that will insure continuity of service and medical care appropriate to the patient's specific needs.

The first step in the development of Richmond's chronic disease control program was the community's early recognition of changes in its public health structure. As the incidence of communicable diseases declined, health problems appeared to be centering themselves largely in the juvenile population and in the aged. In each of these groups, the so-called chronic diseases were demanding increased at-

*Read before the Section on Public Health, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

†From the Department of Public Health, City of Richmond, the Departments of Community Medicine, and Medicine, Medical College of Virginia, and Pine Camp Hospital, Richmond, Va.

tention. Like many American communities, Richmond suddenly became aware of the impact of the aging population, the cost of medical care for its indigent chronically ill patients, and the burden this imposed on health and medical facilities of the area. In the late 1940's this realization caused the community to pause and take stock of its available resources. Lack of facilities for the adequate care of patients with cancer and heart disease served to focus attention of the citizens on the problem. Prior to 1948 patients with terminal cancer were sent to distant private institutions providing such care,—one in Atlanta, Georgia, and one in Philadelphia, Pennsylvania. This situation prompted many public-spirited citizens to pose the question, "Why can't we take care of these cases in Richmond?"

In answer to these queries, the staff of the Health Department suggested that a definitive community study be made of health problems centered around the aged and the chronically ill. The staff realized that the problem of chronic disease was complex; that part of the imbalance in the Department's over-all program was due to the increased emphasis being given to these diseases; and that the organization of a community-wide program for the control of these conditions would necessitate the breaking of many public health traditions. Such a program would call for greater emphasis on the curative aspects of medicine and on rehabilitation. It would also require that the Department assume greater responsibility in the field of medical care.

Since the control of chronic diseases and the planning of essential facilities for their control was too large a task for the official health agency to tackle single handed, the Richmond Area Community Council was called upon for assistance. For the past forty-four years the Council has been a continuous and potent force for community action. Community problems are studied by the Council through the committee structure of its divisions. The committees are composed of a representative cross-section of the community's business, industrial, professional, social and religious groups. In health work it has been the custom for the Department of Health and its advisory Board of Health to work closely with the Council, its member agencies, the Medical College of Virginia, and with the Richmond Academy of Medicine.

One of the first problems encountered in the preliminary planning meetings of the Council was the all too common association of chronic illness with the aging process and with hopelessly incurable conditions. In Richmond, as in other communities, these diseases were thought of only in terms of nursing and domiciliary care. Little attention was given to intermediate type of general hospital care or to the rehabilitative and retraining aspects of these conditions. Even less thought had been given to the preventive aspects of the subject. Because of these general misconceptions regarding chronic illness, the planning group decided to divide the Council's studies into the varied aspects of the problem.

A Study of Needs

As the planning progressed, a pilot committee was established to review the extent of the community problem. For three years, this committee served as a coordinating group for the various special subcommittees. In subsequent meetings it was realized that special subcommittees would be needed to investigate the many and varied aspects of the problem. Accordingly, committees were designated to study the following major areas of the problem: (1) the adequacy of the existing hospital, nursing home and convalescent facilities; (2) the adequacy of the community's rehabilitation facilities; and (3) the adequacy of facilities for home medical and nursing care. In addition to these studies, the planning group undertook to stimulate the development of a long-range program that would provide adequate and permanent facilities.

Earlier Council Committees had already surveyed the total number of available hospital beds. On the other hand, very little was known about the facilities for nursing and convalescent care. To fill in this gap in information a subcommittee made a detailed study in 1947-48 of Richmond's nursing home and convalescent facilities. Although there were 923 beds in these categories, only 683 were available for chronic and terminal care. The remainder (240 beds) were limited in use to tuberculosis. Of more serious importance, the turnover in these beds was relatively insignificant, and the cost for care in the majority of the facilities was beyond the financial means of many in the population.

Early in the course of the Council study it

became apparent that not only were Richmond's existing facilities inadequate, but that certain types of facilities were entirely unavailable. Studies made jointly by the Academy of Medicine and the Community Council on hospital beds and bed-use, pointed out that from 10 to 15 per cent of the general hospital beds were occupied by patients with conditions requiring long-term care. Further, the cost of general hospital care for the long-term case was prohibitive. General hospital rates for the Richmond Area averaged $16.00 to $18.00 per day. Thus, it became apparent that the most acute need was a facility that would provide intermediate hospital care of high quality for the patient after discharge from a general hospital and prior to his transfer to a nursing home, convalescent facility, or to his own home; in short, the community needed a so-called Chronic Disease Hospital.

Recognizing this need, the Council appointed a committee to study ways and means of obtaining such a facility. After a year of intensive work this committee recommended in 1950 that an appropriation of $500,000 be included in Richmond's capital outlay budget, to be matched with federal Hill-Burton funds, to build an intermediate low cost general hospital for the care of long-term cases. Later, as a result of more definitive study, this sum was taken out of the City's five year capital outlay program to be reconsidered at a later date. In retrospect this was a wise decision. Answers were needed to three questions before building such an institution,—(1) How many beds in this category would the community need? (2) Where should such a facility be located? (3) Dependent upon location, what type of construction and equipment would be needed?

As a result of this committee's work, a subcommittee in the year 1953 recommended that consideration be given to the conversion of Pine Camp Hospital to an intermediate general hospital for the care of the long-term case. Pine Camp Hospital was founded in 1911. It has grown through the years from a facility for the isolation for 30 indigent tuberculosis patients to a modern hospital with a 240 bed capacity, a staff of 141 and a budget of $610,000 per annum. The hospital has been approved by the Joint Commission on Accreditation of Hospitals. Concurrent with this recommendation, it became apparent that the Virginia State Health Department was beginning to assume responsibility for the sanatorium care of patients with tuberculosis. Prior to this major cities, in the interest of tuberculosis control, had been compelled to operate sanatoria on the local level.

Conversion of a Hospital to Care for the Chronically Ill

On the basis of the Community Council's recommendation and the State Health Department's acceptance of responsibility for hospitalization of tuberculosis patients, the Board of Health embarked on the gradual conversion of the local sanatorium to a much needed intermediate type hospital for long-term and chronically ill patients. The conversion plan was approved by the Community Council and the Richmond Academy of Medicine.

In the spring of 1955, the Board of Health recommended a somewhat detailed if tentative, schedule of conversion which is quoted as issued to the staff.

Tentative Schedule of Conversion

1. Chronic Disease beds (40) to open July 1, 1955. Cases to be divided among:
   a. Salvageable, nonterminal cases,
   b. Short-term post-hospital discharge cases,
   c. Long-term medical cases with some going to rehabilitation.
2. Handicapped and crippled children (40) beds, tentatively, June, 1956, pending City Manager's approval.
3. Rehabilitation (20) beds, July 1957, pending City Manager's approval.
4. To reach conversion goal by July 1957, reserving 25-35 beds for the isolation of tuberculosis and other communicable diseases.

The Department of Health pointed out to the Administration that good quality medical care could be provided at a lower cost to a group of the population which had not been adequately served in the past. The plan would also permit the continued functioning of the city sanatorium and the preservation of this valuable service to the community. In the chronic illness unit, care could be provided to the patient at a cost of approximately $9.00 a day. This figure would compare very favorably with the $16.00 a day that was charged by the Medical College of Virginia with which the Department contracted for general acute hospital services. In addition to a saving of $7.00 per patient day, the plan would free additional bed space for care of the acutely ill

in the general hospitals of the city. On this basis, the Administration approved the conversion plan for Pine Camp Hospital on a trial basis with July 1, 1955 as the opening date. To show its faith in the plan, the Department deducted a sum of $50,000 in advance from the operating budget of the hosptial. It was anticipated that this amount would be paid by the Medical Aid Bureau of the Department for patient care in the chronic illness unit. Thus, it was assured that the over-all transactions would effect a savings of at least $50,000 from the normal cost of operating the medical care program.

In order to establish the chronic illness unit, a number of changes were necessary in the physical structure of the tuberculosis hospital. Tuberculosis patients were first transferred from the proposed location of the unit and forty new beds were installed on the entire first floor of the central building. The unit was divided into two wings by a temporary partition. One wing was used for colored patients and the other wing was for white patients. It was found that while separate facilities had to be provided, the problem of separating male and female patients was not as great as in the housing of tuberculosis patients. Whenever partitions were needed, they were constructed by the hospital maintenance staff and mounted on casters for greater maneuverability. The partitions could easily be lengthened or shortened by the addition or removal of clamp-on sections.

In order to provide improved access to the building, a concrete ramp was constructed at the end nearest the rehabilitation building. This is used for movement of stretcher and wheel chair patients, and for the convenience of patients on their way to and from the rehabilitation center.

Staffing Requirements

In order to prepare the hospital staff for its new responsibilities, an extensive in-service training program for the medical, nursing, and attendant personnel was conducted. The physicians and nurses who had previously cared only for tuberculosis patients had fallen into a standardized pattern of thinking insofar as the clinical management of tuberculosis was concerned. To be sure, in the course of treating tuberculosis patients, the medical staff had gained experience with a wide variety of patients with other medical conditions and problems, but these in no way compared with the many seriously ill patients who were admitted during the first few months in which the unit was in operation. In addition to more constant nursing attention, these patients required a variety of new and different medications. As a result, a closer supervision of nursing personnel was required.

While the staff anticipated that a quarter of the patients would be incontinent, the average has been closer to 50 per cent. This has presented a problem to nursing morale and has required that more orderlies and nurses' aides be provided to assist the trained nursing personnel. One of the first needs to become apparent was the need for "lifters" in the person of orderlies and nurses' aides. After the unit was opened, all applicants for positions as orderly were judged on their lifting ability as well as for their ability to perform other duties. Later on a hydraulic lifting device was purchased. As experience was gained in the care of chronically ill patients, many previously unanticipated needs for specialized aids and equipment were added.

The entire rehabilitation program at the hospital has been re-evaluated and plans have been made for the expansion of this most important service as the number of patients increases. Consideration must be given to the need for physical therapy and for the extension of this program into the general occupational therapy and vocational guidance program of the general tuberculosis hospital.

It is mandatory that well-qualified medical consultants be available to this type of institution. In the larger general hospital such consultants are on the staff and readily available. Although the chronic disease facility has a well-qualified medical staff, it soon became apparent that there was a need for the services of specialists in internal medicine, physical medicine, psychiatry, and other medical specialties.

The splendid support of the School of Medicine of the Medical College of Virginia and its Hospital Division contributed to the success of this program. Plans are being made by the Medical School to designate faculty members to serve as consultants in medicine, psychiatry, neurology, physical medicine and specialties. Case continuity has been further assured by a change in the record systems of cooperating hospitals and clinics whereby the

patient's records are abstracted and transferred with the patient. When a patient is discharged or dies, the chart returns to the Record Library of the teaching center to be microfilmed and permanently filed. These measures have assured quality of care and the enthusiastic cooperation of students, interns and residents. For the first time, complete case continuity is assured from the home to the clinic, to the "acute hospital," to the intermediate hospital, to the nursing home, or through patient discharge. As the program becomes stabilized, it should provide a rich and realistic learning experience for both medical students and house staff.

Continuity of Care, Costs and Progress

If any one part of the community-wide approach to chronic disease control can be considered more important than the others, perhaps that part is the utilization of usable existing facilities. Through this process and by assuring continuity of medical care, the chronic disease program can be financed at reasonably low cost to the taxpayer. The importance of the proper use of appropriate facilities and of case review and control to insure continuity of care can best be demonstrated by the review of an actual case.

Several months ago, a white man, aged 50, was admitted from the emergency room to the medical service of the Medical College of Virginia Hospital with a diagnosis of cerebral apoplexy. On the fourth day after admission his condition was stabilized and his case was reviewed by the Department of Health's medical coordinator. After consultation with the resident physicians in the Department of Medicine and the Chief of the Department of Physical Medicine, it was agreed that he should be transferred by ambulance to the chronic disease unit of Pine Camp Hospital where his general medical and rehabilitation needs could be provided at a much lower cost per day. At the end of the patient's seventh week of hospitalization, his case was again reviewed and it was agreed that he could be discharged and followed by Richmond's Home Care Service. Accordingly, he was discharged to this service and referred to the Baruch Physical Medical Center for rehabilitation and retraining on an outpatient basis. This individual is presently well on the way to recovery, his work tolerance is established, and he will soon be able to return to his former job on a part-time basis. Through case continuity and transfer to the most appropriate facility at the proper time, the case was managed with economy. Five days of his stay in the medical center were provided at a rate of $16.00 per day; 45 days at the intermediate institution at $9.00 a day; and home care is being provided at a cost of $4.30 per visit. His weekly outpatient visits cost $2.25 per visit.

Comment. The total cost of this case, $490.00, is considerably lower than the total cost of similar cases cared for during the period when Richmond did not have an intermediate hospital facility. Before the opening of the chronic disease unit the cost of such a case at the prevailing general hospital rates of 1953, would have been in excess of $780.00.

Another factor contributing to the success of the program and one of perhaps even greater importance to the support of the Medical Center and the community at large, has been the splendid and enthusiastic acceptance of the conversion program by the members of the Pine Camp staff. Their willingness to tackle the many challenging problems of the transition period, their open-minded acceptance of changes in technics and routine was inspiring. The morale of the entire staff was constantly high and, in turn, served as an inspiration to the other personnel of the institution. The conversion program was undertaken with proper spirit and with enthusiasm. Constructive suggestions were the rule; objections were very rare. In general, the attitude of the entire group was one of "let's try it."

This successful adjustment is due largely to an effective in-service training program and to the spirit of enthusiasm and willingness with which the employees approached the new problems. It was found that the medical staff, graduate nurses and practical nurses all have been able to successfully accept the transition to chronic care and are performing most efficiently. The nurse who has been trained exclusively in a tuberculosis hospital finds it much harder to cope with the other long-term illnesses. In this group, in-service training must be more detailed and lengthy. One of the first principles that must be learned by the nursing staff is that chronically ill patients require more definitive nursing care than do tuberculosis patients. Another principle that should be stressed is that while it may be easier and quicker at first for the nurse to give certain types of care to the patients, it is far better in the long run to teach the patient to care for himself.

The program is not yet fully operative. The highest patient census for the chronic disease unit, to date, has been 29 patients. This limitation has been largely due to the variables of balancing beds on a basis of color and sex. The staff is solving this problem

through the use of movable wall partitions and cubicles. It is reasonably certain, however, that the near future will see the chronic illness unit running at full capacity. Perhaps one measure of the success of any medical care program that is operated by government is economy of operation. The report (financial and patient-stay) at the end of the first quarter was most gratifying. First a savings of $13,585 in the Medical Care budget was effected during the first quarter. The decrease in payments to the Medical College of Virginia were largely accomplished by a reduction in the period of hospitalization of the average patient. During the quarter the stay in the hospital was reduced from a previous average of 9.6 days per patient to 7.3 days,—a net average saving of 2.3 days per patient. Calculated on the contract rate of $16.00 per day, this has amounted to a saving of approximately $37.00 per patient.

Summary

We believe that an intermediate type of general hospital that is capable of providing medical care of high quality to the long-term case is essential to a planned and well-coordinated community-wide medical care program. Further, we believe that the staff of such a hospital which is specifically devoted to the care of the long-term case can provide more considerate care than can be given in the busy general hospital. In the general hospital there is frequently a shortage of beds and the inevitable tendency for staff to become disgruntled over the chronically ill patients and wish that they could be discharged to free the beds for more interesting cases.

The staff of the converted hospital is convinced that it is essential that facilities for the care of the chronically ill be located in close proximity to a medical center or, if there is no medical center available, to a large, well-operated general hospital. The staff also believes that it is important that there be a close working relationship between the intermediate hospital facility and the general hospital wherein appropriate arrangements can be made for consultation and diagnostic services, surgical facilities, and the like. The economy of such an operation consists in holding costly services, such as definitive laboratory and other diagnostic aids, and surgical services to a minimum. Thus, we believe it would be fool-hardy to attempt to convert a tuberculosis sanatorium located in an extremely rural area to serve as an intermediate facility. Perhaps the best use that can be made of such rurally located institutions is their conversion to facilities for convalescent and nursing type of care for the long-term or terminal case.

It is essential that continuity of medical records be maintained and that arrangements be made for the consultants who can coordinate the care of the patients throughout their transfer from hospital to hospital. We also believe that a sound chronic disease program requires careful administrative coordination among the services of the diagnostic and outpatient units, home medical care service, the "acute" and intermediate hospitals and the nursing home. We are also agreed that these can best be achieved through careful community planning and a willingness on the part of all agencies to cooperate in the program. Through the process of community study, duplication of services can also be prevented.

In conclusion, a chronic disease facility permits a saving in expenditures for medical care which, in turn, permits the responsible agency to give better medical care and to increase the scope of its services.

Although the planning of a community chronic disease control program is admittedly a task of great magnitude, it is one that can be solved by nearly every American community if a careful inventory of the community's available resources and usable facilities is made. However, we just as emphatically believe that no one plan fits all communities and that each community can and should tailor its chronic disease program to its own individual and particular requirements.

Discussion (Abstract)

Dr. Lee D. Cady, Houston, Tex. This paper, I think, is an example of careful and meticulous analysis of a situation to find out what a community's problems are, and solving the problems in a sort of slow-motion operating fashion.

If any community, and I am speaking for our own as well, wishes to face such problems which they have right under their own noses, I recommend a careful reading of this paper and isolation of the principles into a little manual, for the community could follow the directions step by step.

So many of the details that come into the tuberculosis problem, the geriatrics problem, and public hospital administration are all common community fac

tors. The author has advised that each community should tailor its plans to its own needs, and the principles are all in this paper. It really concerns three problems that are ever present. I do not believe that we really know yet what all is really happening in tuberculosis. We know that the beds for tuberculosis are not being used as much as previously. We know that patients seem to be getting well, at least they are not dying as they used to. We do not know precisely yet what is going to happen to these same patients in the next few years. But this which we do not know, strangely, is what gives us the empty beds set aside for tuberculosis in these public facilities.

We also know, and this is not a reciprocal relationship unfortunately, that we have an ever-increasing geriatrics problem, which is mounting much more rapidly than the tuberculosis problem is apparently diminishing, thus creating a greater demand for beds. The authors were also concerned very much about whether they should just give these geriatric patients general hospital care and freeze the beds there, or whether they should do something more definitive about that as a problem.

Fortunately, communities are getting around to doing more about the problem of geriatrics or the ill senior citizen, but it is not quite fast enough, I am sure, to eliminate all the various requirements for hospital beds and medical care that are occurring in most communities. I think I should define what we mean by "the intermediate bed:" The patient is too chronically ill and infirm to go home or to a nursing home as we ordinarily understand them out here, and is yet at that stage in which we must say he has had maximum benefit of the hospital. The doctors have done about all they can for him in an "acute" hospital or a general hospital, so that if he remains longer he is keeping some other needy patient out of a bed. If we will then find some way to take care of this patient and give him the medical care he actually needs, it will be a problem solved.

Again, I would like to assure you that when this paper is published, and if you have problems in your own community, that you abstract it and get the principles organized. You will find that you have a manual that will fit most occasions.

I am very happy to have had the opportunity to discuss this paper.

Dr. R. H. Riley, Baltimore, Md. Maryland is very much interested in this paper and its contents since it is trying to solve the problem by building hospitals especially for this group. We have our tuberculosis hospitals and I note what has been said about the death rate from tuberculosis, which is going down in Maryland as it is everywhere else. We are already planning to make use of some of those hospital beds in the tuberculosis hospitals for chronic cases. Now we have two chronic hospitals already completed, with a third one on the way. Our concern is not to make this a dead end for all these people and keep them in the chronic hospitals indefinitely. We are hoping to utilize the nursing homes and maybe take advantage of the Hill-Burton Bill for hospitals, nursing hospitals, and health centers, as a sort of a half-way thing. We hope to give these people all we can at the hospital in the way of treatment, and then when they are sufficiently improved so that we can have their beds for others, we will try to either rehabilitate them or get them at some half-way place, which may be a nursing home.

Now Maryland is set up pretty well to solve these cases. They will still be under the supervision and watchful eye of one of the hospitals. We have in each county a full-time, trained health officer, and we have nurses. And so, when we have a patient going home, he will not be turned loose without some care being given him. We will insist on the health officer getting this patient under the care of a good doctor in the community, and to have the nurses follow his course so a record will be kept of them. With that kind of a setup, we should have a pretty good program especially with more of these institutions that are provided for on a matching basis and which will be constructed, I am quite sure. We have no more almshouses in Maryland, or very few, and the Chronic Hospital Bill was passed with the idea of getting rid of the almshouses where we found many sick people. The counties will still have to have some homes for those who are not sick, but that will not be our problem. Our concern is for the sick individual.

I told you something yesterday about our medical care program in Maryland. We believe that with the medical care program and the chronic hospitals and some of the other things I have indicated, we can take care of the group we have been discussing today.

Dr. Morris Kilgore, Houston, Tex. You mention that you might like to retire to Texas to receive some care in your old age. We have a problem here, and it is very interesting to note the paper discussing the use of tuberculosis facilities for other type diseases. It is so different from our own problem here. We are nowhere near that point of turning tuberculosis facilities into other type facilities, because we are so far behind in our tuberculosis setup, we are in no way keeping up with the tuberculosis problem.

We are also very far behind in the chronic disease type of facility. It is encouraging to note though that the community at large, including our own medical profession, has at last only recently been prodded into some action and we feel that something very constructive is going to come from the interest that has been invoked so far. We certainly appreciate your very fine paper. It has been very stimulating.

Dr. LaFratta (Closing). I know time is getting short, but I want to take one minute to thank Dr. Cady, Dr. Kilgore, and Dr. Riley.

Dr. Cady, you are very kind; I do not know whether this is a manual or not, so to speak. It is a manual for our local area, at least, but whether it would be a manual for the other areas, I cannot answer. But you were kind with your remarks in praising this paper.

Dr. Riley, what you said is very interesting. I do not know how far the program should be developed in its beginning stages. As I said, all we are doing at the moment is bringing in people we think we can help through this intermediate type of care as we might call it. We are not bringing in anyone whom we are going to keep a very long time. As we expand, I suppose that will come, and it is a very fascinating subject to think over since there are so very many possibilities involved.

One thing I would like to mention though,—I know we could discuss this thing at length since it is a fruitful field,—and that is that Richmond is not stopping its tuberculosis control activities. I did want to bring that out. We went into the program of chronic illness hospitalization and we may not be operating as many beds for the tuberculous as we were, but the tuberculosis program in Richmond, and I suppose everywhere else, is drifting into the field and rapidly. I did not want anyone to get the idea that our tuberculosis problem is diminishing in the Richmond area or that we are minimizing it at all.

GOLDEN ANNIVERSARY CELEBRATION, SOUTHERN MEDICAL ASSOCIATION

The Read House, Chattanooga, Tennessee

October 2-3, 1956

The Southern Medical Association is fifty years old. It was born at The Read House in Chattanooga, Tennessee, on Tuesday and Wednesday, October 2-3, 1906. For several years prior to 1906 there had met at Chattanooga a Tri-State Medical Association composed of physicians from Alabama, Georgia and Tennessee. It was the dream of some who had been interested in that organization that it be expanded into a Southern Medical Association.

Dr. G. C. Savage, President of the Tennessee State Medical Association, Nashville, in August 1906 invited the presidents of the state associations of Alabama, Florida, Georgia, Louisiana, Mississippi and Tennessee to send representatives to Chattanooga with the idea of forming a Southern Medical Association.

The group met on Tuesday, October 2, formed a tentative organization and appointed a committee to draft a Constitution and By-Laws, which the committee did that night presenting it at a meeting on Wednesday forenoon, October 3. Dr. J. B. Cowan of Tullahoma, Tennessee, founder of the Tri-State Medical Association, moved the adoption of the Constitution and By-Laws without any change. This was done unanimously and the Southern Medical Association was born.

To commemorate the birth of the Southern Medical Association there will be a Golden Anniversary Celebration at The Read House in Chattanooga Tuesday and Wednesday, October 2-3, 1956. The program for the Celebration will be historical, informative and inspirational. The first activity of the Celebration will be a dinner meeting on Tuesday evening, October 2.

A feature of the dinner meeting on Tuesday evening will be an address by Dr. R. L. Sanders, immediate past-President of the Southern Medical Association, Memphis, on "Fifty Years of Medicine in the South." Dr. Sanders graduated from a medical school in Nashville early in 1906, his fifty years of active practice running concurrently with the fifty years of the Southern Medical Association.

Dr. Dwight H. Murray, President of the American Medical Association, Napa, California, will represent the American Medical Association, speaking Tuesday evening. The Woman's Auxiliary of the Southern Medical Association and of the American Medical Association will be represented on the program. Recognition will be given to those who had a part in the formation of the Southern. The Celebration will be concluded with further recognitions at a session Wednesday forenoon closing with the unveiling of a plaque commemorating the fifty years of the Southern Medical Association to be presented to The Read House.

Dr. Guy M. Francis, President of the Chattanooga and Hamilton County Medical Society, will give a short address of welcome and bring greetings from the local medical society. Dr. W. Raymond McKenzie, President of the Southern Medical Association, Baltimore, Maryland, and Dr. J. P. Culpepper, Jr., President-Elect, Hattiesburg, Mississippi, will officially participate in the Celebration program.

The Council of the Southern Medical Association at the annual meeting in Houston in November 1955 in authorizing this Golden Anniversary Celebration named Mr. C. P. Loranz, Birmingham, Chairman of the Celebration Committee. It will be recalled that Mr. Loranz has been with the Association in an active capacity for forty-four of the Association's fifty years.

At this meeting in 1906 a committee on organization was formed. The committee report included an invitation "to join with us in making this one of the most influential

Continued on page 1027

Maryland's Home and Office Medical Care Program*

R. H. RILEY, M.D., *Baltimore, Md.*

ONE OF THE GRAVEST RESPONSIBILITIES of our democracy is to find solutions to serious social problems, solutions that fit our people, our institutions and our heritage. Maryland, for the past ten years, has been solving the problem of the provision of home and office medical care for its low income citizens, with a free choice of physician, without Federal aid, and through facilities available in the community.

Maryland is a comparatively small state with a population of approximately two and a half million; a little less than half of the people live in the City of Baltimore and the others in the 23 counties. Each county has an organized county health department and a full time medical officer who serves in the dual capacity of county and deputy State Health Officer. The counties vary greatly, from a small agricultural unit bordering on the Chesapeake Bay in the southeast where over a third of the population is Negro, through the large centrally located counties with rapidly growing urban areas around the District of Columbia and Baltimore City, to the rugged mountainous counties in the western part of the State where there are almost no Negroes. The City of Baltimore, with its independent health department, is a well-known medical center with two large teaching hospitals.

Because of differences in the type and availability of medical manpower and facilities and of local conditions and mores, two distinct medical care plans are in operation in the State, both financed by appropriations of the State legislature:—one, a program in the counties administered by the Bureau of Medical Services and Hospitals of the State Department of Health, in conjunction with the Deputy State Health Officers under a fee-for-service system of payment; the other in the City of Baltimore administered by the Medical Care Section of the Baltimore City Health Department under a capitation system of payment for physician and clinic services. Both programs were designed to complement, and not to supplement, the many other existing medical care services rendered by public and private agencies and civic minded individuals.

It is significant that the initial impetus for the establishment of these programs came from the Medical and Chirurgical Faculty of Maryland (the State Medical Society). The first step was an open letter in 1939 sent by the Faculty to the Maryland State Planning Commission, which is a public agency created by law to deal with "subjects affecting the health and welfare of the people." A committee of the Planning Commission undertook a survey of the medical facilities and needs of the citizens of the State. Among other recommendations, this committee proposed the plan which became known as the "County Medical Care Program." The committee recommended that responsibility for administration should rest with the State Health Department, breaking with the usual tradition of placing responsibility in the Welfare Department. The plan for the counties received the unanimous approval of the Medical and Chirurgical Faculty in 1944, enabling legislation was passed in 1945, and the program began operation in July of that year.

The program in Baltimore City developed later. In 1944, a special subcommittee of the Committee on Medical Care of the Planning Commission surveyed the medical care needs of the City of Baltimore and proposed a medical care plan for recipients of public assistance in the city to be administered by the City Health Department. This plan also had the approval of the medical society before it began operation in August 1948.

In the counties, the program serves the indigent, that is the recipients of public assist-

*Read before the Section on Public Health, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

ance and the medically indigent, defined as normally self-supporting persons who are unable to meet the cost of medical care. Determination of eligibility for the indigents is handled by the Department of Welfare since recipients of public assistance are automatically eligible for the program. The determination of eligibility for the medically indigent, a variable and somewhat elusive segment of the population, is the responsibility of the county health departments. For administrative purposes, established income scales, graduated by size of family and living costs in the counties, serve as standards for determinations of eligibility for medical indigency. A family of four, for example, living in the more prosperous counties is eligible if their income is less than $1,452 per year. County health officers have the prerogative of granting exceptions to these income scales in the face of unusual medical or social circumstances.

In most instances, medically indigent persons apply for enrollment in the face of actual medical need, and so represent an adversely selected group. They are enrolled for various periods of time, depending on medical need and social and economic factors, but are limited to a maximum coverage of six months without reapplication. The indigents are enrolled for a period of six months but are recertified if still on the welfare rolls. Each person or family accepted under the program is furnished with an identification card which indicates the expiration date of coverage. The program in Baltimore City has so far been limited to the indigent, with the Department of Welfare handling the determination of eligibility; certification is issued for a maximum period of three months, subject to recertification if the individual continues on the welfare rolls.

The programs cover about 2 per cent of the population of the State, with an average combined enrollment of, roughly, 50,000 people. The cost of providing service, exclusive of administrative costs, is running at about $1,500,000 per year, the equivalent of 50 to 60 cents per capita for the entire population.

As was mentioned earlier each program was specifically planned for the locale in which it was to operate. In the counties where the specialized services of hospital outpatient departments are not generally accessible or available, the plan is centered in the services of physicians in private practice. The program offers physician's service in the home or office with provision for consultations by specialists and nonspecialists, and x-ray and laboratory service performed in the physician's office when this is not available through health department facilities. Somewhat limited dental services are included, with primary emphasis on relatively complete service for children and young adults. Dentures are provided; however, authorization for this comparatively expensive item must be obtained in advance. Drugs and some medical supplies as prescribed by the physician are also provided.

The patient needing care seeks service from the physician, dentist or pharmacist in the community. He has complete freedom of choice and likewise the doctor, dentist or pharmacist may accept or reject the patient as with private cases.

Payments for services rendered are made monthly on the basis of reports of service in accordance with fee schedules which were developed with the full cooperation of the State's medical, dental and pharmaceutical associations. A physician, for example, is paid $2.00 for an office call and a specialist receives $10.00 for a consultation. Dentists are paid $2.00 for a single extraction or a silver amalgam filling, and varying amounts for other services up to a maximum of $85.00 for a full set of upper and lower dentures. Pharmacists are paid for prescriptions which they have dispensed on a schedule covering, for each prescription, wholesale ingredient cost, container charge if necessary, and a mark-up allowance for professional service. This mark-up is a basic 30 per cent of cost with a minimum allowance of 40 cents for uncompounded and 60 cents for compounded prescriptions. Fee schedules are uniform throughout the counties. No professional participant is permitted to make supplementary charges to the patient for services rendered under the plan.

The day to day operation of the program is in the hands of the county health departments, and it is the county health officer and his staff who daily meet and solve the countless minor and major problems which inevitably arise in a program dealing with more than 20,000 patients and over 1,400 professional participants in a year. Of invaluable help to the program has been the Council on

Medical Care, a representative advisory body set up by law which meets monthly to advise on the program's operation and to recommend formulation of policy.

In Baltimore City, in contrast to conditions in the counties, hospital outpatient departments are relatively accessible and have traditionally provided both emergency and day to day care to ambulatory patients in the lower economic strata. The city program utilizes the integrated services both of private practicing physicians and of hospital outpatient facilities. It offers to its beneficiaries physicians' service in the home and office, and consultant, diagnostic and special treatment services in hospital outpatient clinics. Limited dental care is provided as well as drugs and some medical supplies prescribed by physicians.

Medical care clinics have been set up in the outpatient departments of seven large hospitals under contract between the Commissioner of Health of Baltimore City and the parent hospital. Clients of the Welfare Department are assigned by the Medical Care Section of the Baltimore City Health Department to a medical care clinic, according to the location of their residence. At the clinic, each new patient is given an initial examination, any necessary emergency service, and is asked to designate the private practicing physician of his choice. The physician is contacted by the clinic and, if he agrees to accept the patient, serves as the patient's family doctor with the facilities of the Medical Care Clinic and the outpatient department of the parent hospital available for supporting services. The physician is sent copies of the medical care clinic's findings. Prescribed drugs and medical supplies are provided by the neighborhood or hospital pharmacy. Most dental services are rendered by dental clinics at the hospitals and are limited primarily to extractions and emergency care. A recent development is the establishment of a special dental clinic in a health department facility to provide more inclusive care. Each eligible person is kept supplied with an up-to-date card, showing the period of his eligibility, the name, address and telephone number of his physician, and the name of his medical care clinic.

Payments for services rendered by medical care clinics and physicians are made on a capitation basis. For each public assistance client assigned to its medical care clinic, hospitals are paid quarterly in advance at the rate of $10.00 per year. Physicians receive $7.00 per year. For dental service, hospitals are paid on a fee-for-service basis with a ceiling set at the rate of $1.00 per person assigned per year. Pharmacists are paid according to the same fee schedule that is in use under the county program.

The medical care clinic directors have considerable autonomy in carrying out the clinic functions and are primarily responsible to the board of the parent hospital. The Medical Care Section of the City Health Department handles the day to day contacts with participating physicians and pharmacists. The Medical Care Clinics submit quarterly reports on the type and volume of services rendered, and each year submit cost statements to substantiate expenditures under the capitation system of payment. Physicians report quarterly on convenient report forms detailing the number and type of call rendered to each patient under their care. Special studies, usually on a sampling basis, are made from time to time on various aspects of the program's operation.

The cost of providing coverage to the welfare recipients in the fiscal year ending June 30, 1955, was surprisingly close under both programs, despite the fact that the services offered and the method of payment differ. In the city it cost $26.11 per person year of coverage, in the counties, $26.38. The cost of prescribed drugs is the most directly comparable item under the two programs. In Baltimore City this amounted to $8.51 per person year of coverage and in the counties $9.96. Costs under the county program for the medically indigent run much higher, since these people represent an adversely selected medical risk. For each twelve months of coverage for the medically indigent costs were $45.91, compared to $26.38 for the indigent.

Professional participation in both programs has been at a satisfactory level. About 300 physicians participate in the Baltimore City Program. Many Baltimore City physicians are inaccessible to patients under the program because of the geographical concentration of the indigents in certain areas of the city.

In the counties, between 800 and 900 physicians participate during a year. In the rural areas there is nearly 100 per cent par-

ticipation by physicians in private practice; however, this percentage drops considerably in the more urban centers.

Although both programs have become an accepted part of the Medical Care pattern in Maryland, they have by no means solved all of their problems. The adequacy of appropriations is always a potential source of difficulty. During the past year, for example, each program resorted to waiting lists for persons qualifying under the eligibility standards, as there were insufficient funds to cover all eligible persons. At various times in the past, under the county program, prorating of payments to physicians and dentists has been made, usually at 70 per cent of the face value of the bills. Every year it is a very real and vital challenge to gain the understanding and support of the public at large and of the State legislators for budget requests.

Another serious problem is presented by expenditures for prescribed drugs. Not only has the average cost of a prescription shown a steady increase over the years, but the absolute and relative amounts spent for prescribed drugs have also shown steady increases. A partial explanation of this trend is no doubt the change in prescribing practices of physicians, reflecting the accelerated development of new, frequently elegant and usually expensive preparations. Nevertheless, when prescriptions are studied in detail, concern is felt over such questions as the cost of many proprietary drugs compared to that of their less expensive U.S. or National Formulary equivalent or counterpart, over the quantity of a drug sometimes prescribed in a single prescription or the number of refills authorized. The problem seems basically an educational one, centered in the need to convince physicians, participating in a tax supported program, of the necessity for limiting prescribed drugs to the most economical minimum consistent with a patient's needs.

Various educational approaches have been tried, and recently in Baltimore City a formulary was introduced to serve as a guide to participating physicians. Under the county program, policy regulations for dispensed drugs have been made more stringent. Despite these efforts, the ideal solution has not been found to the pressing problem of expenditures for drugs. Other aspects of both programs are being actively studied as a basis for future development.

The success that both programs have so far enjoyed is due in large measure to the effective cooperation between professional groups, their individual members, and a public agency. Both programs aim to fulfill a threefold responsibility: to the patient to see that he obtains adequate medical care; to the professional participant to see that he receives a reasonable reimbursement for his contribution; and to the public to insure that tax funds are expended to the maximum benefit of the greatest number of needy citizens. We look confidently to the future, with high hopes for continued development and improvement both in quality and scope of services provided.

Discussion (Abstract)

Dr. William J. Peeples, Rockville, Md. I would like to congratulate Dr. Riley on an excellent paper. Dr. Riley, as you know, has been State Health Officer of Maryland for the past 27 years and is retiring from his position at the end of this year. I think he is to be congratulated for doing an excellent job and constructing an excellent medical care program.

This unique program of medical care is designed to fit the needs of Maryland and to complement medical care services already available. The service is comprehensive, well planned, well received, by the recipients, the medical profession and the general public. There are about 900 doctors participating in this program.

Dr. Riley stated in the last paragraph of his fine paper that this program accomplished three objectives: (1) to insure adequate medical care to those in need of the service; (2) to adequately compensate the physicians for their professional services rendered the patient; and (3) to assure the public that the tax dollar is expended to the maximum benefit of those who require medical care.

A fourth responsibility is also evident in the design of the Maryland program, that of preserving and encouraging the free enterprise of medical practice. This important concept is supported by evidence that visits to physicians in their office outnumber 4 to 1 the number of visits to hospital clinics and other types of outpatient services. The doctor-patient relationship is not disturbed, and the patient has no sense of dependency created since arrangements between the patient and the doctor are made entirely by them. In this program, there is an average of only 5.8 visits a year to the physician and 5.5 prescriptions per indigent person a year. Before the program was put into operation, there was some concern among physicians of the State that abuse might be widespread. Experience has calmed these fears.

Throughout the South there are several types of medical care available:

(1) Categorical Medical Care Programs, or those fulfilling medical care in a field of need, such as, cancer, tuberculosis, services for crippled children, mental hospital medical care, vocational rehabilitation and others. Each state generally has provided services of this nature.

(2) Hospital Clinics and Outpatient Services,—local governments provide medical care for the indigent and medically indigent through these facilities. In some areas, medical schools have provided, as part of a teaching curriculum, medical care programs to serve those in need. Richmond, Virginia, has such a program administered by the local health department, which provides home and clinical medical care and nursing services, physiotherapy, social service, occupational therapy and rehabilitation, along with diagnosis and treatment. These services in the main usually do not provide care for the rural indigent individual.

(3) Insurance for Medical Care,—limited in most of the Southern states to Blue Shield types of insurance which provide predominantly surgical care, but little or no medical coverage. Insurance, of course, does not help the indigent or medically indigent class of patients, as they cannot afford the premiums which, when compared with the quoted costs in the Maryland program of $26.00 per year for the indigent patient and $45.00 per year for the medically indigent patient, would be considerably higher and still would not provide the really necessary coverage. Some counties in the South, however, have provided hospitalization for the indigent citizens on a group hospital insurance plan.

(4) Industrial Programs for Medical Care,—these usually incorporate the voluntary insurance type of medical care along with other services provided by industry. Such programs, of course, apply only to the working individual and some members of his family, and do nothing for the indigent patient who really needs medical care.

(5) The Private Physician—The private physician bears most of the load for the indigent medical care and collects nothing. He must charge more to those who are able to pay to meet the expense of caring for the indigent free of charge. This makes the physician, in essence, a tax collector.

An item of importance is getting away from strictly symptomatic treatment and considering what steps can be taken to rehabilitate the patient from a medical standpoint. Thirty-seven per cent of all patients in the Maryland program were between 15 and 65 years of age; 35 per cent were under 15 and only 28 per cent above 65. Assuming then that the 28 per cent of the indigent recipients are over 65 and cannot be medically rehabilitated, 72 per cent in the younger age groups can be treated with medical rehabilitation in mind.

I believe the most important point mentioned in Dr. Riley's paper was that the Maryland program was instituted by action and leadership of the State Medical Society. The medical profession must take the lead in designing programs of medical care to meet the needs of the indigent and medically indigent in their own localities according to the facilities, personnel, and funds which are available to meet the demands peculiar to their own State or political subdivision. There has been too much planning of programs involving the medical profession by political interest, voluntary and welfare agencies, rather than by the medical profession, which should rightly take such leadership rather than having poorly designed, often expensive programs, forced on it through public demand.

Dr. Riley is to be again congratulated on a very fine paper and a very constructive bit of leadership in establishing this excellent medical program.

Golden Anniversary Celebration, *Continued from page 1022*

and important bodies of medical men in the United States." Those who know the Southern Medical Association realize that that is exactly what has happened. The Southern Medical Association today is truly "one of the most influential and important bodies of medical men in the United States."

A cordial invitation is extended to the members and friends of the Southern Medical Association to celebrate the birth of the Association by attending the Golden Anniversary Celebration.

Preceding the Golden Anniversary Celebration will be the annual meeting of the Tennessee Valley Medical Assembly with a splendid scientific program all day Monday, October 1, and until late afternoon Tuesday, October 2. In addition to the scientific program, entertainment features have been arranged for both the physicians and the visiting ladies. For the program of the Assembly see advertising page 63, rear form, of this issue.

An Evaluation of Pentothal Sodium for Delivery*

HUGH A. McALLISTER, M.D., and CHARLES E. FLOWERS, JR., M.D.,†
Chapel Hill, N. C.

The acknowledged dangers of thiopental anesthesia make this study of its use in obstetrical narcosis of interest. The authors report no difficulties in either the mothers or children.

THE LACK OF QUALIFIED ANESTHESIOLOGISTS OR ANESTHETISTS is a fundamental deficit in our obstetrical care. We have attempted to overcome the discrepancy between the coverage of surgical anesthesia and obstetrical anesthesia by the use of Trilene, pudendal block and natural childbirth. These are valuable adjuncts to relief of obstetrical pain. However, the majority of hospitals in this country have a significant number of patients who prefer general anesthesia during parturition.

This report concerns the use of Pentothal Sodium in 7,793 deliveries between the years of 1948 and 1955. During the last five years 82 per cent of all the deliveries at the Robeson County Memorial Hospital have been done under thiopental anesthesia (Table 1). The percentage of use signifies the acceptance of the method by the physicians in the hospital and the patients in the community.

Pharmacologic Action of Pentothal Sodium

Pentothal Sodium is a thiobarbiturate which is primarily a parasympathomimetic hypnotic. But when used in conjunction with nitrous oxide, oxygen, cyclopropane, ether and conduction anesthesia, it becomes a useful agent in the practice of anesthesia.

It would seem that Pentothal Sodium would have an extremely limited place in obstetrical anesthesia. Being a parasympathomimetic, laryngospasm could be easily produced by the perineal distention at the time of delivery. Being primarily a hypnotic, it would seem that profound cerebral depression would be necessary to alleviate the pain of parturition. Being a potent hypnotic, fetal depression could be an undesirable complication. Apparently, however, Pentothal is a useful agent in obstetrics.[1-3]

When Pentothal Sodium is used intermittently and intelligently in patients who have not ingested a recent meal and have had parasympathetic depression by hyoscine, laryngospasm is not a significant complication. There were no maternal deaths due to anesthesia and no serious laryngospasms in this series. Conservative doses of 5 per cent Pentothal give sufficient cerebral depression to alleviate pain but apparently not sufficient to depress the more primitive medullary centers. Solutions of 2.5 per cent are less satisfactory and are not recommended for thiopental hypnosis for delivery.

The lack of fetal depression is more difficult to explain. The rapid passage of thiobarbiturates across the placenta is fact.[4,5] The rapid disappearance of thiopental from the blood stream and its concentration in body fat is likewise well established[6] (Fig. 1).

Table 2 presents the infant and maternal blood levels of the anesthetic 21 patients delivered at varying periods of time and employ-

TABLE 1

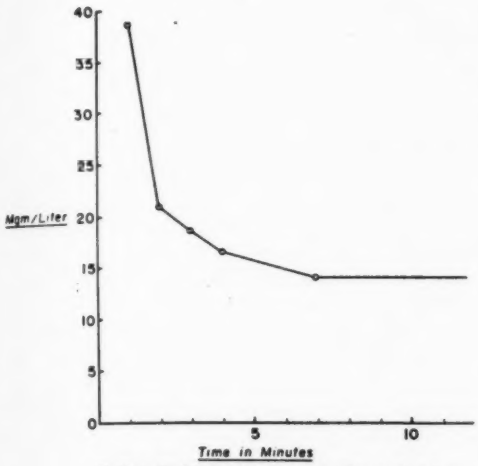
DELIVERIES UNDER PENTOTHAL SODIUM AT THE ROBESON COUNTY HOSPITAL

Year	*Total Deliveries In Hospital*	*Percentage Under Pentothal*	*Number Under Pentothal*
1948	1,086	6	73
1949	1,066	21	226
1950	1,281	54	691
1951	1,691	82	1,399
1952	1,655	81	1,347
1953	1,721	91	1,581
1954	1,743	83	1,453
1955	1,345	76	1,023
Total	11,588		7,793

*Read before the Section on Obstetrics, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

†From the Robeson County Memorial Hospital and the Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, Chapel Hill, N. C.

FIG. 1



Sodium Pentothal disappearance after acute injection of 300 mgm of Sodium Pentothal in 1½ min.

ing limited doses of Pentothal. The analysis was made by extraction of plasma by chloroform and subsequent extraction of chloroform by sodium hydroxide. Readings were made at 305 mu on a Beckman Model DU spectrophotometer.[7] Petroleum ether extractions were not used, since short time intervals were involved.[8]

It is apparent that there is no real correlation between the infant blood level of Pentothal and the reaction time of the infant. Pentothal rapidly crosses into the fetal circulation without predictable blood levels. Equilibrium between maternal and fetal blood develops quickly, though the blood levels are variable. It is not surprising that there is not always complete correlation between maternal and fetal blood levels. The intermittent injection of the Pentothal, the rapid disappearance of Pentothal in the tissue spaces and fat, and the unpredictable placental circulation at the time of delivery can account for these variations.

Not so easily understandable is the fact that despite almost equal blood concentrations of Pentothal in the mother and fetus, a vigorously crying infant can be delivered of a mother who is asleep. To explain this one must think hypothetically. Thiobarbiturates rapidly leave the blood stream and enter tissue spaces.

If only a small amount of Pentothal is used, time is not a factor in fetal depression, since the Pentothal will leave both maternal and infant circulation rapidly. However, if large intermittent doses are employed over prolonged periods of time, tissue saturation may occur and Pentothal can be responsible for depression in the infant. In this series of Pentothal anesthesia, small doses were used for short times.

A second factor may be the presence of drug tolerance and adaptability in the new-

TABLE 2

CORRELATION OF DOSAGE, BLOOD LEVEL AND INFANT REACTION TIME IN PENTOTHAL ANESTHESIA

Time	*Dose mg. of 5% Pentothal*	*Blood Level Mother mg./L*	*Blood Level Infant mg./L*	*Breathing Time Seconds*	*Crying Time Seconds*	*Delayed Apnea*	*Delivery*
1	150	4.3	0.0	30	45	No	Breech
1.5	250	10.8	8.0	30	30	No	Spontaneous
2	100	2.5	0.2	60	120	No	Breech
2	150	5.0	5.0	15	15	No	Spontaneous
2	200	9.0	26.0	15	15	No	Spontaneous
2	200	11.0	15.0	15	15	No	Low forceps
2	200	19.0	12.0	60	60	No	Spontaneous
2	250	4.8	0.2	40	60	No	Low forceps
2	450	10.8	5.0	60	120	No	Spontaneous
2.5	100	4.7	0.4	60	120	No	Spontaneous
3	150	1.0	2.0	120	120	No	Spontaneous
3	200	36	24	15	15	No	Spontaneous
3	250	29	35	15	45	No	Spontaneous
3	350	38	27	60	60	No	Spontaneous
4	200	12.1	4.6	15	15	No	Spontaneous
4	300	25	37	45	60	No	Spontaneous
5	250	17	15	60	60	No	Spontaneous
6	250	36.5	24	30	60	No	Spontaneous
8	300	15	42	15	15	No	Spontaneous
15	200	12.5	13	5 min.	8 min.	Yes	Spontaneous
18	450	10.1	4	60	120	No	Spontaneous

TABLE 3

AN ANALYSIS OF 150 PENTOTHAL ANESTHETICS FOR DELIVERY

Race:		*Analgesia:*		*Infant Death:*	
White	70	None	10	Hydrocephalic monster	1
Colored	25	Nisentil	7	Macerated stillborn	1
Indian	55	Demerol	21	Premature separation of placenta	1
Parity:		Demerol-Scopolamine	112		
Primipara	33	*Duration of Anesthesia to Delivery:*		*Dosage 5% Pentothal:*	
Multipara	117	One Minute	5	100 to 150 mg.	27
Maturity:		2 Minutes	15	150 to 200 mg.	31
Term	147	3 Minutes	46	200 to 250 mg.	50
Premature	3	4 Minutes	39	250 to 300 mg.	15
Method of Delivery:		5 Minutes	17	300 to 400 mg.	16
Spontaneous	131	6 Minutes	14	400 to 450 mg.	9
Low forceps	13	7 Minutes	5	Above 450	2
Breech extraction	6	8 Minutes	5		
		Above 8	4		

Infants With Delayed Breathing Time and Crying Time

Name	*Weight*	*Analgesia*	*Breathing Time*	*Crying Time*	*Delivery*	*Duration Anesthesia*	*Dosage Pentothal*
D.S.	3100	Demerol 150 mg.	1 min.	3 min.	Spontaneous	5 min.	200 mg.
M.L.	2750	Demerol 200 mg.	1 min.	5 min.	Spontaneous	1 min.	200 mg.
A.E.	2950	Demerol 100 mg.	30 sec.	5 min.	Spontaneous	3 min.	200 mg.
M.S.	2900	Nisentil 100 mg.	5 min.	6 min.	Spontaneous	3 min.	200 mg.
A.P.	3400	Demerol 100 mg.	1 min.	6 min.	Low forceps	11 min.	450 mg.
R.M.	3700	Demerol 100 mg.	1 min.	10 min.	Spontaneous	4 min.	200 mg.
F.B.	3600	Demerol 100 mg. Nisentil 90 mg.	3 min.	13 min.	Spontaneous	3 min.	100 mg.

born infant. Possibly the primitive urge to establish extrauterine respiration is profound.

Analysis of Cases

Table 3 presents a critical analysis of 150 unselected cases of Pentothal anesthesia. The majority of the patients were multiparas at term who delivered spontaneously after having received Demerol-Scopolamine analgesia. However, there were 33 primiparas, 3 premature infants, 13 low forceps and 6 breech extractions. There were 3 infant deaths which were not related to anesthesia. There were 7 infants who had delayed breathing and crying time. Three of these infants' mothers had received excessive doses of analgesic drugs, patients F.B., M.L. and M.S. The fact that only 5 per cent of the infants required resuscitation may be a sampling error. However, this low figure may be indicative of the safety of the technic. Moreover, in the entire series of 7,793 deliveries, there were no infant deaths that were attributable to anesthesia.

It is evident that the majority of the patients received less than 300 mg. of Pentothal and were anesthetized less than 5 minutes prior to delivery.

Prerequisites for Pentothal Anesthesia

There are certain prerequisites for the safe administration of Pentothal Sodium in obstetrics:

1. The patient should not have ingested solid food less than two hours before the onset of labor.

2. Oxygen should be administered with Pentothal Sodium, since the arterial oxygen saturation may fall during its administration.[9] The use of a mixture of 2 liters of nitrous oxide and 2 liters of oxygen is a valuable adjunct to Pentothal anesthesia in obstetrics.

3. Persons who are responsible for Pentothal anesthesia should have both the materials necessary and the technical knowledge to treat laryngospasm.

4. The administration of Pentothal Sodium should be delayed until the total amount of Pentothal which is given prior to delivery should not exceed 0.5 Gm.

Method of Administration

One gram of Pentothal is mixed with 20 cc. of distilled water to make a 5 per cent solution. The resulting solution contains 50 mg. per cu. mm.

The average initial dose should not exceed 200 mg. in the first 30 to 60 seconds. Anesthesia is maintained with intermittent doses of 50 mg. No attempt is made to predetermine the total dose required. There is wide varia-

tion in the individual tolerance to thiobarbiturates.

Pentothal anesthesia in obstetrics should be used in combination with a pudendal block, or at least local perineal infiltration.

Essentially all of these 7,793 obstetrical anesthetics were administered by delivery room nurses, since Robeson County Hospital, like many hospitals in this country, does not have anesthesia coverage for obstetrics. Pentothal was used in all of the major obstetrical complications and emergencies, including cesarean section, breech extraction and eclampsia. When the delivery room nurse must serve as the anesthetist, and when narcosis is desired, properly administered Pentothal is safer, much faster, and far more esthetic than the use of open drop ether, chloroform and gas oxygen combinations.

Summary

A sizable series of obstetrical cases in which Pentothal anesthesia was used is presented. An analysis of the cases is made. A discussion of the basic pharmacologic action of Pentothal in obstetrics is attempted. It is felt that this drug deserves further use as an obstetrical anesthetic. Apparently, fetal depression from Pentothal is more a product of total dosage than the duration of anesthesia. The problem of infant adaptability to various anesthetic and analgesic drugs is an enticing problem and requires clarification.

The authors are grateful for the cooperation of the medical staff of the Robeson County Memorial Hospital and the technical assistance of Miss Genevieve Lowry, North Carolina Memorial Hospital, Chapel Hill, N. C.

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Discussion (Abstract)

Dr. L. W. Fabian, Durham, N. C. The manner in which Dr. Flowers' presentation has been made leaves little to be criticized from the anesthesiologist's point of view. He has stressed the use of minimal doses of Pentothal given at a time when delivery of the infant is imminent thus diminishing the likelihood of fetal cardiovascular and respiratory depression. His results speak for themselves in demonstrating the value and safety of this technic. Important too is his emphasis on the possible maternal complications following administration of Pentothal, notably laryngobronchospasm and hypotension.

If the above factors are kept in mind the supplementary use of Pentothal following pudendal block can be a valuable adjunct in obstetrical delivery where mild hypnosis and analgesia are desirable. As mentioned by Dr. Flowers, specially trained personnel must, if at all possible, be present during these procedures to aid in prevention or treatment of Pentothal-induced cardiorespiratory complications.

Drs. McAllister and Flowers are to be congratulated on this work and on their careful evaluation of the use of Pentothal in the field of obstetrics.

Dr. C. Gordon Johnson, New Orleans, La. I have read with considerable interest the report on Pentothal anesthesia in obstetrics by Drs. McAllister and Flowers. They have presented an astounding number of deliveries with this type of anesthesia. I am sorry, however, that they have analyzed only 150 cases in detail. One cannot fail to note that of the 150 cases analyzed, 131, or 87 per cent, delivered spontaneously. The question then arises, could not the greater part of these spontaneous deliveries have occurred satisfactorily without the use of any so-called terminal anesthesia?

The Tulane Obstetrical service at Charity Hospital of Louisiana, at New Orleans, is fortunate to have the Department of Anesthesia headed by Dr. John Adriani. Dr. Adriani is opposed to the use of Pentothal in obstetrics because of the danger of maternal complications and fetal depression. He does not allow it to be used by nurse anesthetists except under supervision of a physician anesthetist, since he feels very strongly concerning the safety of Pentothal even in the hands of trained anesthetists. One must remember that laryngospasm and apnea are serious complications that can occur with Pentothal anesthesia, and are controlled only with difficulty even by experienced anesthetists.

We feel that this anesthetic agent, if used at all, should be administered only in small dosages, and for short periods. Its use should be avoided in eclamptic toxemias and many other complications of pregnancy. We also feel that it should be used only by persons trained in the management of air-way and resuscitative equipment.

Finally, we make a plea for more spontaneous deliveries, especially in multipara, without the use of any so-called terminal anesthesia.

Dr. Flowers (Closing). I would have been disappointed if my discussers had not been critical and added a note of caution concerning the use of Pentothal Sodium in obstetrics.

I am in complete accord with Dr. Adriani's criticism of the use of Pentothal anesthesia for delivery. We are emphasizing, however, Pentothal hypnosis, with a local block, not anesthesia; and we have presented a sizable series of cases.

I agree with Dr. Johnson that it would have been advantageous to have critically analyzed more than 150 cases. However, personnel were not available for the collection of this data until six weeks ago. We are planning to obtain more detailed data concerning infant reactions to various anesthetic and analgesic drugs and to attempt further correlations between infant reaction times and blood levels of obstetrical analgesics and hypnotics.

If an anesthesiologist, or even a qualified anesthetist, were available in every delivery floor in this country, this paper would need only to concern itself with the pharmacology of Pentothal and the placental transfer of the agent. However, such qualified personnel are not available in many of our hospitals in the South. It is thus my considered opinion that Pentothal hypnosis with pudendal block may be a useful technic in these institutions. It is evident that some women request and earnestly desire narcosis at the time of delivery. When feasible it would seem only human to honor their wishes. Certainly, Pentothal is safer, far more esthetic, than open drop ether with its obstructive breathing, slow induction and post-delivery nausea.

Dr. McAllister and I are grateful to the Obstetrical Section in granting us the privilege of presenting this material and for the timely and critical remarks of our discussers.

Golden

Anniversary Meeting

Southern Medical Association

Washington, D. C.

November 12-15, 1956

A Simplified Technic of Suprapubic Prostatectomy*

J. R. REAGAN, M.D., F. W. TAYLOR, M.D., and R. E. HIGGS, M.D.,
Wichita Falls, Tex.

By their technic the authors believe they reduce postoperative bleeding to a minimum and have a most favorable postoperative morbidity and mortality.

THE TECHNIC OF SUPRAPUBIC PROSTATECTOMY to be outlined is not considered as original with us. It is a technic combining various maneuvers which we feel simplify this procedure.

Technic

The patient is draped with the external genitalia exposed so that ready access to the rectum is available. We have recently begun to use the O'Conner drape which we feel obviates an increased chance for infection during the introduction and removal of the left index finger from the rectum during the enucleation.

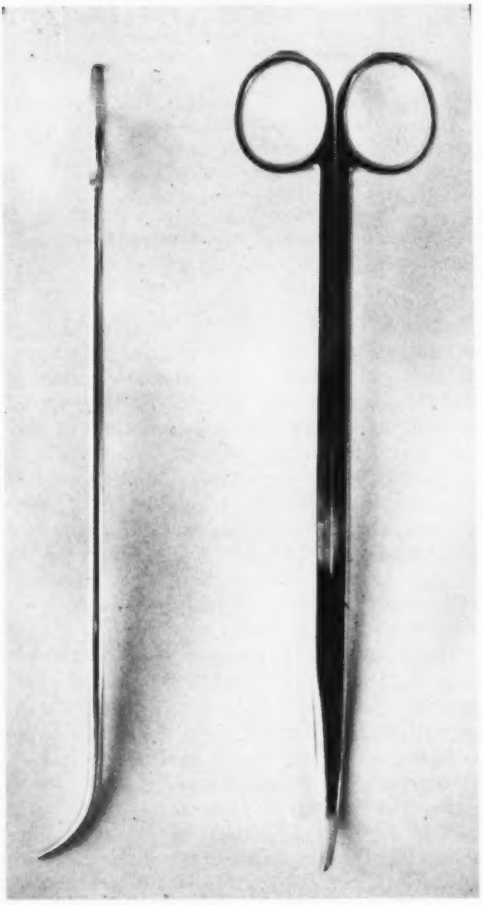
After the patient is draped, the bladder is overdistended, utilizing a 1:5000 solution of Zephrin-chloride. It has been our experience that when the bladder is opened as high in the dome as conceivable, the bleeding is minimized and closure is more easily obtained. A rather small incision is made immediately above the symphysis pubis, measuring approximately 8 cm., extending as closely to the symphysis pubis as is possible. In those instances in which the abdomen is pendulous the patient is placed in the Trendelenburg position. After the space of Retzius is entered the bladder dome is grasped with two Allis forceps, and a bistoury blade is used to make a puncture wound in the dome of the bladder. This is then enlarged by manual dilatation in a circular manner, and the Zephrin-chloride solution is aspirated. The enucleation is then done. When the O'Conner drape is used, one can insert a finger, if needed, into the rectum with relative ease to augment the sharp dissection of the internal vesical orifice and to rule out the possibility of leaving residual prostatic tissue in place. Following the enucleation, a self-retaining bladder retractor is put in place and a tonsil-tip suction apparatus is placed within the prostatic fossa. If bleeding is extensive, a small pack is placed within the prostatic fossa. Continuous suction is utilized by the assistant with one hand, and with the other a malleable retractor is placed against the base of the bladder in order to visualize the internal vesical orifice to a greater extent. Any excessive tissue at the internal vesical orifice is then trimmed away, and usually a V-shaped wedge of tissue is removed from the posterior aspect of the vesical neck utilizing the Reagan bladder scissors (Fig. 1).† Long Allis forceps are then applied to the bleeding points. A figure-of-eight suture is taken to control these arterial bleeding points. A No. 24 Foley urethral irrigating catheter with a 30 cc. balloon is then put in place; the balloon is distended to 30 cc. and pulled down against the internal vesical orifice. Traction is utilized only if the bleeding is marked. Oxycel gauze and other similar hemostatic preparations are no longer used except in very rare instances, since their aid in helping control hemorrhage, in our experience, is questionable and we have had several instances in which incompletely absorbed gauze has acted as a nidus for stone formation, or has precipitated acute urinary retention. A No. 18 Foley suprapubic catheter is put in place, and the bladder is then closed in two layers of continuous chromic No. 0 catgut. Interrupted chromic No. 0 catgut is used on the anterior layer of the rectus sheath and triple No. 0 plain catgut in the subcutaneous tissue.

It has been our experience that in utilizing the suprapubic Foley catheter in the first 24

*Read before the Section on Urology, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

†The Reagan Bladder Scissors are available from the Codman and Shurtleff, Inc., 104 Brookline Avenue, Boston 15, Mass.

FIG. 1



Reagan Bladder Scissors

hour period, any excessive bleeding or tendency for the catheters to become occluded is markedly reduced by virtue of one of the catheters usually draining satisfactorily. A slow continuous drip of sterile water is utilized for constant catheter irrigation. The suprapubic catheter is removed at the end of 24 hours; this does not seem to appreciably increase the incidence of suprapubic fistulae. The abdominal incision is kept rather small so that the incidence of postoperative incisional hernia is diminished, as well as the fact that one can use no more room through the skin than is available in the incision in the dome of the bladder.

The question of hemostasis is very frequently discussed in suprapubic prostatic surgery, and there are many who feel that suturing at the internal vesical orifice is of no avail. We see many rather large arterial bleeders at this point which, if not sutured, would certainly precipitate prolonged bleeding and would certainly complicate the postoperative convalescent period. Our average patient having a suprapubic prostatectomy does not need to be transfused. The use of a gauze pack within the prostatic fossa in those instances in which the adenoma is large and the bleeding profuse, certainly aids in the control of hemostasis by virtue of allowing venous oozing to come under control during the suturing of the internal vesical orifice and by keeping the field more clear.

The urethral catheter, in our series of approximately 1,100 cases, is usually removed at the end of four days. The largest adenoma successfully removed by this procedure weighed 408 grams. In those instances in which the adenoma is small, it frequently is of some benefit to place an Allis forceps at the posterior aspect of the internal vesical orifice, and to remove a V-shaped wedge of tissue at this point prior to the enucleation. This has been especially useful in rather small glands in which multiple calculi were present and when it was felt that they could be better handled suprapubically than transurethrally. (We prefer transurethral resection of the prostate gland in cases in which the tissue removed is expected to be less than 30 grams and in carcinomatous processes. Approximately 50 per cent of our prostatic surgery is performed transurethrally.)

We feel that the points outlined in this procedure, as well as early ambulation, definitely reduce the postoperative complications as well as shorten the hospital stay. Our patients are usually dismissed on the seventh postoperative day, and our mortality rate is being maintained at less than 1 per cent.

Summary

A presentation of our method of suprapubic prostatectomy is given in this paper with emphasis placed on:

1. Overdistention of the bladder prior to opening,

2. Sharp dissection of the internal vesical orifice, utilizing the Reagan bladder scissors,

3. Suturing of arterial bleeders at the internal vesical orifice,

4. Suprapubic catheter drainage for 24 hours and

5. Early ambulation.

We feel that the above points have definitely aided in lowering operative mortality and morbidity. Also, they aid in making this a more versatile procedure so that vesical calculi, many of the vesical neoplasms, and other entities seen concomitantly can be treated at the same time without unduly increasing the operative time and morbidity.

Discussion (Abstract)

Dr. James C. Cope, Columbia, Mo. Dr. Taylor has demonstrated a very neat method of suprapubic prostatectomy. There are several points Dr. Taylor has covered to which I wish to add emphasis. First is that of routine suprapubic drainage of the bladder following open prostatectomies. It has been my experience that this drain acts as a safety valve and prevents later complications in wound healing and fistula formation. A suprapubic tube which keeps the bladder decompressed and protects the suture line until the tissues have had a chance to seal themselves, will seldom result in an annoying suprapubic fistula but will always prevent the formation of deep abscesses and tissue necrosis due to the extravasation of urine throughout the operative site. If this tube is removed within 24 to 48 hours after operation, healing will not be delayed and in many cases suprapubic drainage will cease more quickly than if total closure of the bladder is practiced.

The second point he makes, and to which I wish to add emphasis, is the necessity for doing a wedge resection at the bladder neck, particularly in the case of a small gland. In a transurethral procedure this is easily accomplished but in the suprapubic procedure it is easily forgotten or not used, with the result a second procedure must be done to remove a portion of the bladder neck which contracts. Occasionally it is necessary to remove a portion of the interureteric ridge as well, which may also produce an obstruction. I make it a practice to remove this wedge of tissue in every case where the bladder neck seems tight and where the enlargement of the prostate has not been primarily of the intravesical type.

The third point I wish to emphasize is Dr. Taylor's indications for doing a suprapubic prostatectomy, that is any prostate in which they believe over 30 grams of tissue are present. Here I would like to quote Dr. Harry Culver from the *Surgical Clinics of North America*, (Vol. 30, p. 27) published in 1950: "A vigorous man in the fifth decade, with a grade II or III hypertrophic gland should have a complete removal of all hyperplastic tissue to insure probable permanent results. Usually this can be done only by enucleation. Some resectionists may approach complete removal of hypertrophic tissue in such a case but any amount of this tissue remaining renders the patient a candidate for further trouble, since his life expectancy is 20 years or more, and it cannot be anticipated what may happen if even small amounts of such tissue are not removed."

I believe that in the past too much emphasis has been placed on length of hospital stay and amount of tissue removed, rather than on the remote result and the amount of tissue which remains after the transurethral resection. Certainly today, when the length of human life is stretching toward the 100 mark, we are seldom justified in doing any procedure which will not give a good, permanent result.

Several years ago I collected a series of my own prostatectomies and found that approximately 10 per cent had had previous surgery, and of this number who had had previous operations by far the most common type of surgery was transurethral resection. In one case I recall a patient had had two previous transurethral resections and I removed 80 grams of adenomatous tissue by the perineal route.

The fourth point which I would like to stress is the adequate hemostasis at the operating table. This is a principle of surgery and prostatectomy is no exception. There is no reason why any patient should leave the operating room with active bleeding from the prostatic fossa.

In conclusion, I would like to state that Dr. Taylor has shown us that the hospital stay and the operative mortality of the suprapubic prostatectomy need be no greater than that of any other type of prostatic surgery, and, as previously indicated, these two facts free us to view only the remote result which, in my opinion, is determined solely by whether or not the entire prostatic adenoma is removed. While it is hardly apropos here to discuss other methods of prostatectomy, we should remember that there are a number of methods, all of which may be good in a given case. In the final analysis our best results will be obtained when each case is individualized and the type of surgery selected is based upon the merits of the case at hand. Too frequently we hear of all prostatectomies being done by a certain method. To my mind this is unphysiologic and is wasteful of the experience which we have gained.

Finally, I would like to quote Scott, from the *Yearbook of Urology for 1951:* "Considerable progress could be made if urologists would agree that no single operation for the removal of the obstructing prostate applies to every patient. The type of operation should be chosen on the basis of the patient's condition, diagnosis, sexual potency, and the size of the prostate. Certainly all young urologists should be taught all methods."

Dr. Jarratt P. Robertson, Birmingham, Ala. Approximately 60 years ago Fuller and Freyer used the suprapubic approach to remove the prostate. The perineal technic was worked out by Dr. Hugh Young and there has been little change in it since that time.

There have been numerous changes in the technic of suprapubic prostatectomy during the past 30 years. Few urologists today use the Pilcher bag and traction technic to control hemorrhage. Harris of Sydney, Australia, in 1927 to 1930, reported his results of suprapubic prostatectomy with primary closure of the bladder. Rose of St. Louis reported a technic of suprapubic prostatectomy with closure of the bladder without suprapubic or urethral catheter drainage. Millin of England perfected the retropubic approach with primary closure of the prostatic capsule. Hand and Sullivan, in 1951, reported the use of the retropubic

approach with a vertical incision extending from midway of the prostatic capsule through the first one centimeter of the bladder with primary closure.

Since the work of Harris numerous technics, catheters and hemostatic agents have been devised to control the hemorrhage accompanying suprapubic prostatectomy. The retropubic and suprapubic approach do not carry with them as high an instance of loss of sexual function and urinary incontinence as does the perineal approach. More prostates weighing 40 grams or more are being removed by suprapubic or retropubic prostatectomy than ever before, as morbidity, mortality and hospital days compare favorably with those obtained by either the perineal or transurethral approach. In the suprapubic, the retropubic or retrosuprapubic, the majority of urologists attempt to control all possible bleeding by fulguration and ligation to avoid the use of hemostatic agents and traction catheters.

Drainage by suprapubic catheter should not be employed unless excessive bleeding is anticipated. Inserted through a small opening above the bladder incision, if removed in 24 to 48 hours it does not delay healing. This catheter is placed for suprapubic drainage and evacuation of blood clots and I feel should be a 26 F - 5 cc. Foley and not an 18 F - 5 cc. Foley as advocated by Dr. Taylor. Multiple catheters in the bladder usually increase spasm and this increases hemorrhage and sedation. Therefore a suprapubic catheter should not be placed unless excessive bleeding at operation warrants its use.

The retrosuprapubic prostatectomy (vertical incision in the prostatic capsule and bladder) I feel offers the best approach to control hemorrhage at the operating table. One is looking directly into the vesicle orifice. Bleeders are easily seen and ligated or fulgurated. I place a figure-of-eight traction suture of plain catgut at 3 and 9 o'clock. They are used to pull open the bladder neck. At 5 and 7 o'clock a figure eight suture is placed to control the main bleeding. A wedge of tissue is removed at 6 o'clock. A running suture of a plain catgut is placed in each side of this incision. Additional sutures are placed above the traction sutures if needed. The needle comes out deep in the prostatic fossa in all these sutures. This type of suturing controls all bleeding at the bladder neck, does not constrict the vesicle orifice as they are separate and not one continuous suture. Due to the satisfactory exposure only a few minutes are required to place these sutures. The double balloon hemostatic bag will control the bleeding from deep in the prostatic cavity. It will seldom be necessary to place a suprapubic catheter for drainage if this type of hemostatic suturing is employed.

In a few cases of suprapubic prostatectomy I have sutured for the arterial bleeding at the vesicle orifice and then employed transverse sutures to close the bladder neck with primary closure of the bladder after the technic of Theodor Hryntshak (Runtschak).

Of all the operations for removal of the prostate and technics to control hemorrhage, I believe the retrosuprapubic approach with suturing of the vesicle orifice and the use of the double balloon hemostatic catheter, with primary closure of the vertical incision in the prostatic capsule and bladder is the best. It decreases the operative time and blood loss, and offers the best postoperative hemostasis.

Drs. Reagan, Taylor and Higgs have presented a series of approximately 1,100 cases. Their mortality rate, days of postoperative catheter drainage and hospital stay compare favorably with any similar size group of cases, regardless of the type of operation employed.

Dr. F. W. Taylor (Closing). I would like to reiterate and mention one or two things. One of them is that the urethral catheter is removed on usually the fourth postoperative day. We feel that this definitely decreases the instance of urethral stricture. One reason that I mentioned the fact of doing relatively small glands this way is by virtue of trying to do all prostatic surgery, when at all possible, in 45 minutes or less. This procedure usually runs about 35 minutes.

Digitalis Toxicity in Chronic Cor Pulmonale*

GEORGE L. BAUM, M.D., MORRIS M. DICK, M.D.,
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The authors have shown that patients having cor pulmonale with severe pulmonary insufficiency may react unfavorably to digitalis. Its use should be only in conjunction with treatment of the physiologic abnormalities of the lungs.

THE USEFULNESS OF THE DIGITALIS DRUGS in the therapy of chronic cor pulmonale has long been a controversial subject. In 1934 White[1] advocated the administration of digitalis in the presence of chronic cor pulmonale with congestive failure. He further stated that "a therapeutic test of digitalis in cases of chronic bronchitis and emphysema is often helpful, since heart weakness is easily masked by the pulmonary condition." The importance of therapy of the underlying lung disease was stressed. On the other hand, Friedberg[2] in 1950 claimed that ". . . digitalis is usually not beneficial but should be given a trial."

Ferrer and her co-workers[3] in the same year reported on the hemodynamic effects of intravenous Digoxin in chronic cor pulmonale. When congestive failure was present there was a moderate rise in cardiac output and a slight but significant rise in pulmonary artery pressure. The right ventricular end-diastolic pressure decreased. After a period of combined therapy directed toward the underlying pulmonary disease as well as Digoxin, there was subsidence of the evidences of cardiac failure and a return of the cardiac output to normal. The arterial oxygen saturation improved. Pulmonary artery and right ventricular pressures returned to near normal levels. There were no pulmonary artery or right ventricular pressure changes when the patients without congestive failure were similarly studied.

Similar studies were reported in 1952 by Gray and others,[4] using intravenous lanatoside C. The expected increase in cardiac output and right ventricular pressure was elicited. However, some cases exhibited an increase in the right atrial mean pressure and in the right ventricular end-diastolic pressure. There were a few cases in which the arterial oxygen saturation fell during the procedure. There was impairment of ventilatory function in other cases.

Segal and Dulfano,[5] after reviewing the literature, concluded that digitalis or its derivatives should be included in the management of chronic cor pulmonale in the presence of heart failure.

Recent reports indicate a mounting frequency of digitalis intoxication.[6,7] This is ascribed to the manner of digitalis usage, the employment of the purified glycosides, and to salt-depleting measures. Flaxman,[8] in 1948, described 30 cases of digitoxin poisoning unrelated to type of heart disease. However, there were no cases of chronic cor pulmonale in this series.

Lown and Levine[6] emphasized the relationship of the therapeutic and toxic effects of digitalis to the potassium concentration in the myocardial cell. Anoxia, edema, acidosis, and prolonged exercise are known to cause cellular depletion of potassium.[9-12]

At this hospital, 44 consecutive patients with congestive failure secondary to chronic cor pulmonale were treated with digitalis. Seven developed evidence of toxicity. Those seven were all acutely ill, cyanotic and markedly dyspneic. It was, therefore, deemed worthwhile to employ the acetyl-strophanthidin tolerance test as described by Lown and Levine[13] in an attempt to determine the sensitivity to digitalis in a similar group of patients. The purpose of this study was to ascertain any correlation between sensitivity to this agent and various physiologic measurements relating to pulmonary function.

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†From the Medical Service, Veterans Administration Hospital, Coral Gables, Fla.

Materials and Methods

Nineteen patients from the Medical Service of the Coral Gables Veterans Administration Hospital are the subject of this report. In each instance a diagnosis of chronic pulmonary emphysema with chronic cor pulmonale had been made. Each patient had been evaluated with respect to complete history and physical examination, electrocardiography and roentgenography of the chest. Cardiac fluoroscopy was performed in 16 subjects. The remaining three were too ill for this examination.

Sixteen patients were evaluated under basal conditions in the laboratory. The remainder were studied at the bedside when urgent consultation was requested. Maximum breathing capacity, vital capacity (V.C.) and three-second vital capacity (3″ V.C.) were measured one day prior to the procedure with a 9 liter respirometer. These observations were expressed as per cent of predicted normal.[14] The significance of timed vital capacities has been reported elsewhere.[15] Venous pressure (V.P.) was done with a water manometer, using an 18 gauge needle in an antecubital vein 5 centimeters below the horizontal plane of the anterior surface of the sternum at its fourth costochondral junction.

Arterial blood was collected through an indwelling needle in the brachial or femoral artery. Carbon dioxide content and oxygen content and capacity were determined on the Van Slyke-Neill apparatus.[16] Duplicate analyses checked within 0.2 volumes per cent. Blood pH was performed with a Cambridge pH meter. Blood carbon dioxide tension (pCO_2) was determined with the aid of a nomogram based on the Henderson-Hasselbach equation.[17]

These measurements, except for the maximum breathing capacity, were obtained just prior to the administration of acetyl-strophanthidin. The drug was given according to the method of Lown and Levine[13] in the first 15 cases. One and two-tenths milligrams were diluted to 20 cc. in 5 per cent glucose in water. Five cubic centimeters of this dilution were given intravenously every five minutes until either a therapeutic or a toxic response was achieved. This dose is considered to be that which is tolerated by the nonsensitive patient. Electrocardiographic tracings were taken before each injection and 10 minutes after the last injection. The various physiologic measurements were repeated 10 minutes after the last injection. When the total dose was given as a single injection in four cases, the measurements were repeated 12 minutes later.

None of the patients selected for study had received any digitalis for at least three weeks.

TABLE 1

DESCRIPTION OF CASES

Chronic Pulmonary Emphysema	19
Bleeding gastric ulcer plus CO_2 intoxication	1
Bilateral bronchiectasis	2
Metastatic renal carcinoma to lung plus diffuse pulmonary fibrosis	1
Bronchial asthma	3
Primary	12
Total	19

Results

A summation of the clinical diagnosis is presented in table 1. Each case had a major diagnosis of chronic pulmonary emphysema. One suffered from severe carbon dioxide intoxication together with a massive gastrointestinal hemorrhage from which he succumbed. Bilateral bronchiectasis was present in two cases. One patient also had pulmonary fibrosis together with pulmonary metastases from a renal carcinoma. Bronchial asthma was present in three cases. Twelve patients were classified as "primary" pulmonary emphysema.

The results of the ventilatory studies are given in table 2. The mean values for maximum breathing capacity, vital capacity and three-second vital capacity were 24, 49, and 30 per cent, respectively. The greater decrease in maximum breathing capacity is typical of the marked ventilatory defect seen in chronic diffuse obstructive pulmonary emphysema.[18] These studies were performed in 14 cases, the remainder being too ill for satisfactory cooperation.

TABLE 2

VENTILATORY STUDIES (14 Cases)

	Mean	*S.D.**
Maximum Breathing Capacity (% Pred.)	24	± 7
Vital Capacity (% Pred.)	49	± 19
3″ Vital Capacity (% Pred.)	30	± 12

*S.D.—Standard deviation.

TABLE 3

ARTERIAL GAS STUDIES (18 Cases)

	Mean	S.D.
O_2 content (vol. %)	15.5	± 3.2
O_2 capacity (vol. %)	18.3	± 3.6
O_2 saturation (%)	81	± 11
CO_2 content (vol. %)	58.4	± 6.7
pCO_2 (mm. Hg.)	49	± 11
pH	7.42	± 0.02

The average values for the arterial blood gases just prior to the administration of acetyl-strophanthidin are given in table 3. Arterial blood was collected in 18 cases. The mean oxygen saturation was 81 per cent, with a range of 63 to 93. The mean value for pCO_2 was 49 mm. Hg. with a range of 27 to 88.

Electrocardiographic evidences of sensitivity to acetyl-strophanthidin were detected in six of these 18 patients. Table 4 indicates that the initial arterial blood oxygen saturation was below 75 per cent in five of these six cases. One of these (S.G.) exhibited a significant fall in the arterial blood oxygen saturation, from 71 to 59 per cent, after the intravenous administration of diluted acetyl-strophanthidin. Each patient in the sensitive group presented an arterial pCO_2 above 50 mm. Hg., with no significant change after the drug was given. Three of this group were too ill for ventilatory studies. The remainder exhibited greatly reduced values for the vital capacity and three-second vital capacity. Venous pressures were significantly elevated in three of the four in whom it was measured. Each patient in the sensitive group was clinically considered to be in cardiac failure. The effects of acetyl-strophanthidin on the various physiologic measurements were poorly correlated with the presence or absence of digitalis sensitivity. These effects will be given later in this presentation.

TABLE 4

ACETYL-STROPHANTHIDIN SENSITIVITY PRESENT

	Art. O_2 sat. % Pre	Post	Art. pCO_2 mm. Hg. Pre	Post	V. C. (% Pred.) Pre	Post	3" V. C. (% Pred.) Pre	Post	V. P. mm. H_2O Pre	Post
A. G.+	63	#	60	54	•	•	•	•		
W. S.+	73	78	50	52	43	•	31	•	180	85
S. G.	71	59	53	51	36	32	23	21	95	80
J. M.+	87	91	50	48	30	29	19	20	220	190
W. S.+	55	54	54	53	•	•	•	•	120	220
G. M.**	73		88		•	•	•	•		

#Blood clotted in syringe
•Too dyspneic or uncooperative
**Semicomatose
+Increased dyspnea after acetyl-strophanthidin

TABLE 5

NO ACETYL-STROPHANTHIDIN SENSITIVITY PRESENT

	Art. O_2 sat. % Pre	Post	Art. pCO_2 mm. Hg. Pre	Post	V. C. (% Pred.) Pre	Post	3" V. C. (% Pred.) Pre	Post	V. P. mm. H_2O Pre	Post
B. H.**	73	74	53	51	42	40	25	28	60	35
J. G.	77	78	42	42	61	72	41	44	50	50
J. R.	81	78	38	39	43	41	28	21	90	90
M. F.+	83	82	62	59	#	#	#	#	250	160
R. W.	85		41		84		51		85	
A. J.**	89	89	43	44	15	20	15	20	50	260

**Increased dyspnea after acetyl-strophanthidin
#Too dyspneic
+Auricular flutter

Twelve patients presented no evidences of acetyl-strophanthidin sensitivity. The data collected on these patients are presented in tables 5 and 6. Only one case in this group (B.H.) manifested an arterial blood oxygen saturation below 75 per cent. The arterial blood pCO_2 was above 50 mm. Hg. in only two cases (B.H. and M.F.). Two patients in this group (M.F. and G.F.) showed evidences of right sided heart failure with elevated venous pressures. The vital capacity and three-second vital capacity measurements were quite variable, ranging from 15 to 84, and 15 to 55 per cent, respectively.

Of the entire group of 14 patients so measured, a significant increase in vital capacity after acetyl-strophanthidin administration was obtained in only one patient (J.G.). The remainder showed minor changes in the vital capacity and three-second vital capacity.

Changes in venous pressure were unrelated to presence or absence of sensitivity to acetyl-strophanthidin. After administration of the drug, two subjects (M.F. and W.S.) exhibited a pronounced fall in venous pressure. Four patients (W.S., A.J., W.W. and G.F.) showed

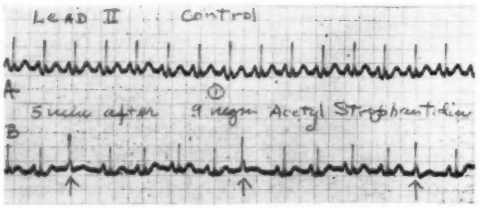
TABLE 6

NO ACETYL-STROPHANTHIDIN SENSITIVITY PRESENT

	Art. O_2 sat. % Pre	Post	Art. pCO_2 mm. Hg. Pre	Post	V. C. (% Pred.) Pre	Post	3" V. C. (% Pred.) Pre	Post	V. P. mm. H_2O Pre	Post
T. K.	89	94	36	35	49	55	35	39	60	35
D. C.	90	89	49	46	38	37	21	21	98	85
W. W.	91	88	48	48	71	59	55	55	60	100
J. H.	93	91	27	25	63	57	32	36	50	30
G. F.**	93	91	49	48	31	34	18	21	110	240
A. P.	82	84	46	44	34	33	25	28	20	20

**Increased dyspnea after acetyl-strophanthidin

FIG. 1



G. M. (A) Lead II Control record—sinus tachycardia. (B) 5 minutes after administration of 0.9 mg. acetyl-strophanthidin; frequent premature ventricular contractions.

a significant rise, while slight decreases were noted in four cases. The remainder did not demonstrate significant changes in venous pressure.

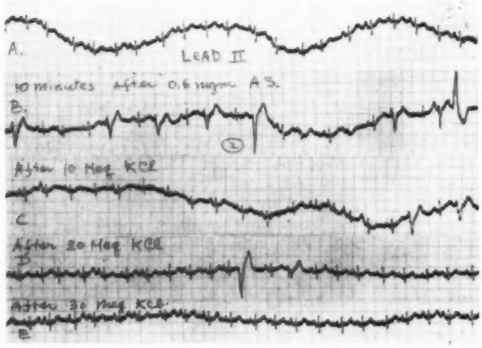
The pronounced drop in arterial blood oxygen saturation in the patient S.G. was the only significant change in blood gas composition after acetyl-strophanthidin administration.

Dyspnea became more pronounced after the administration of the drug in four subjects.

One additional patient, C.B., who was markedly dyspneic and cyanotic, also presented evidences of acetyl-strophanthidin sensitivity. Physiologic data were not obtained in this case.

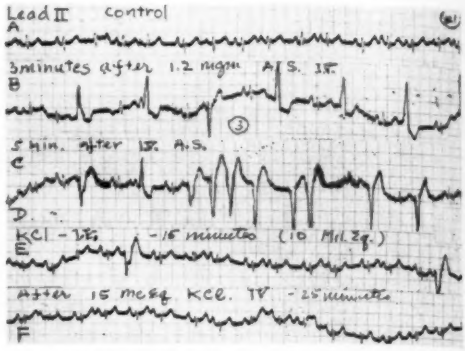
Figures 1 to 4 are electrocardiographic tracings indicating the presence of acetyl-strophanthidin sensitivity in patients G.M., W.S., W.S., and C.B. W.S. was studied on two different occasions three months apart.

FIG. 2



W. S. (A) Lead II Control record—sinus tachycardia with occasional premature auricular contractions. (B) 10 minutes after administration of 0.6 mg. acetyl-strophanthidin; frequent premature ventricular contractions of multifocal origin. (C, D, and E) Gradual decrease in frequency of premature ventricular contractions following treatment with KCl.

FIG. 3



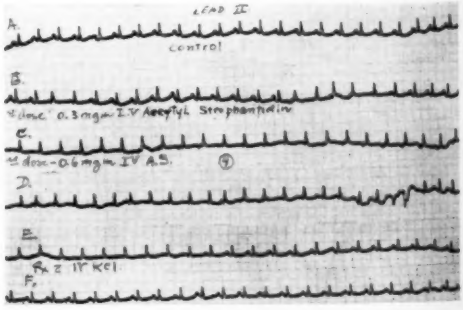
W. S. (3 months later). (A) Lead II Control record—sinus tachycardia. (B) 3 minutes after 1.2 mg. acetyl-strophanthidin intravenously (as a single dose); frequent premature ventricular contractions with transient bigeminy rhythm. (C) 5 minutes after 1.2 mg. acetyl-strophanthidin; transient ventricular tachycardia. (E, F) Gradual reduction and elimination of premature ventricular contractions following KCl treatment. The recovery from the arrhythmia after potassium chloride administration is further confirmation of presence of digitalis sensitivity.

Comment

The increased respiratory embarrassment that occurred in four patients after administration of acetyl-strophanthidin was not correlated with any significant change in vital capacity or three-second vital capacity. The increased dyspnea may have been the result of an increased pulmonary blood flow through a restricted vascular bed with diminution in elasticity of the lungs. Gray and his co-workers[4] reported an increased functional residual capacity in some cases after administration of lanatoside C.

The significant elevations of venous pres-

FIG. 4



C. B. (A) Lead II Control record—sinus tachycardia. (B, C, D) Development of transient auricular ventricular dissociation with nodal rhythm, wandering pacemaker and premature ventricular contractions after 0.6 mg. acetyl-strophanthidin administered intravenously. (E, F) Recovery from ectopic rhythm after treatment with KCl.

sure occurring in four cases after digitalis administration is of considerable interest. Liebow[19] has discussed the development of the bronchopulmonary venous collateral circulation in chronic pulmonary emphysema. It is conceivable that an increased pulmonary vascular pressure after acute digitalization may favor an increased flow from the pulmonary veins to the bronchial veins, which drain into the right side of the heart. Thus the systemic venous pressure may be at least temporarily elevated after administration of the drug.

The significant decline in arterial oxygen saturation that occurred in one case after the administration of acetyl-strophanthidin may be due to increased shunting of blood through non-ventilated areas of the lungs.

Pronounced arterial blood oxygen unsaturation and elevation of the carbon dioxide tension were present in those cases exhibiting acetyl-strophanthidin sensitivity. Either one or both of these factors may contribute to the alteration of the myocardial threshold for digitalis sensitivity.

Beneficial effects may accompany these deleterious effects. There was a marked decrease in venous pressure in two subjects, and a slight fall in four subjects, possibly related to better emptying of the right ventricle.

This study indicates that patients with chronic cor pulmonale with severe pulmonary insufficiency may exhibit harmful effects, including sensitivity, secondary to the administration of digitalis. These patients usually present manifestations of hypoxia and carbon dioxide retention. It is therefore concluded that digitalis should only be employed when the cardiac failure is pronounced and when the patient fails to respond to intensive therapy directed toward improving pulmonary function. When digitalis is employed, it should be given slowly and cautiously, and only in conjunction with measures concerned with the underlying pulmonary disease. These include intermittent positive pressure breathing, the cautious administration of oxygen, avoidance of heavy sedation, elimination of secretions, bronchodilators, and antibiotics.

Summary

1. Physiologic measurements before and 10 to 12 minutes after the administration of 1.2 mg. of acetyl-strophanthidin intravenously to 18 patients with chronic cor pulmonale are reported.

2. A fall in venous pressure occurred in six cases.

3. Deleterious effects in some cases included development of unusual digitalis sensitivity, rise in venous pressure, and a decrease in arterial oxygen saturation.

4. Sensitivity to acetyl-strophanthidin occurred in the presence of pronounced arterial oxygen unsaturation and carbon dioxide retention.

5. The relationship of these findings to therapy was discussed.

The authors are indebted to Mrs. Catherine Osgood, Mrs. Ardys Baretta, and Mr. Mark Wynn for their invaluable technical assistance.

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Discussion (Abstract)

Dr. James K. Alexander, Houston, Tex. I think that Drs. Baum and Dick are to be commended on a

most interesting study. It seems to me that in trying to evaluate these results and in trying to determine what shall be our course of action in the clinical management of these problems, it is well to remember the changes which occur in association with cor pulmonale, secondary to chronic emphysema before the digitalis preparation is administered. As you will recall, these patients characteristically show a tendency to increased cardiac output which is also associated with pulmonary hypertension and elevation of the right ventricular diastolic pressure. The pulmonary venous pressure in these patients, as indicated by measurements of "pulmonary capillary" pressure, is usually normal, indicating that there is no element of left heart failure present.

Now, in association with acute digitalization in such cases, one finds that the same changes occur in cor pulmonale as may be associated with other types of heart failure after the administration of digitalis, that is, the cardiac output tends to rise and the right ventricular diastolic pressure tends to fall. As Dr. Baum has indicated, this is also associated with an increase in the degree of pulmonary hypertension which is present. Like Dr. Baum, I believe that the tendency for some of these patients to develop dyspnea in association with the rapid digitalization is the result of transient increase in pulmonary hypertension. Later on, as those patients are followed, it is found—let us say a period of two or three weeks later—when they are restudied, that their tendency to pulmonary hypertension is much less, the output has fallen considerably, the right ventricular diastolic pressure now approaches normal, and the elevated blood volume has also returned toward a normal value.

Like most, although the subject is a controversial one, I believe that I would subscribe to the view that digitalis is a useful adjunct in the therapy of congestive failure associated with severe chronic obstructive emphysema. I believe that because of the worthwhile therapeutic effect which may be achieved after a period of two or three weeks on the drug.

Now, so far as I am aware, there are no studies to tell us what may be the circulatory changes associated with the administration of digitalis to the point of toxicity in patients with severe emphysema, or in patients with cor pulmonale secondary to severe emphysema. I would assume that in these individuals, one probably has the same thing occurring as in the normal individuals, that is, a tendency to a lowering of the cardiac output and perhaps a further rise in the right ventricular diastolic pressure. It seems reasonable to suppose that such an event would be associated with further alteration in the disturbed alveolar ventilation perfusion relationship in these patients, making for further anoxia, further CO_2 retention. I would conclude, then, as I believe that Dr. Baum has concluded, from these studies that one should be reasonably certain before the digitalis preparation is administered to a patient with chronic emphysema that the signs and symptoms, that is, elevated venous pressure, and preferably edema, of right heart failure are present and clearcut. I would feel, secondly, that a rapidly-acting preparation is to be avoided if possible, unless extenuating circumstances mitigate this decision; and, thirdly, it would seem advisable to exercise extreme care to avoid overdigitalization in these patients with resultant lowering of cardiac output, alteration in alveolar ventilation perfusion relationships, and further anoxia and CO_2 retention.

Dr. Baum (Closing). I want to thank Dr. Alexander for his discussion. It seems that we are in agreement. We also feel that digitalis is a very useful drug when it is used intelligently. We agree that no rapidly-acting digitalis preparation should be used. Digitalization should only be employed after all measures designed toward improvement of pulmonary ventilation have been utilized.

A Case of Adenocarcinoma of the Thyroid Metastasizing to Bone:

Sixteen-Year Follow-Up*

JULIAN E. JACOBS, M.D., *Charlotte, N. C.*, and
JAMES J. CONNERS, M.D.,† *St. Louis, Mo.*

This case illustrates the low-grade level of malignancy occasionally encountered in the metastatic lesions of carcinoma of the thyroid gland.

THE INCIDENCE OF METASTASIS OF CARCINOMA OF THE THYROID GLAND to bone is secondary only to metastases from cancer of the breast and prostate. The incidence of cancer of the thyroid as brought out by Lahey and his associates and George Crile, Jr., is much higher than the incidence reported in vital statistics. Lahey[1] reports 10.05 per cent incidence of malignancy in discrete adenomas of the thyroid and 0.62 per cent in multiple adenomatous goiters. Crile[2] reports 24.5 per cent incidence of malignancy in nontoxic solitary tumors of the thyroid and 10.9 per cent in nontoxic nodular goiters. Thus, pending the time when the problem of prevention of thyroid carcinoma will have been satisfactorily solved on an etiologic basis, or when Lahey's dictum of early and universal removal of all discrete adenomata of the thyroid is accepted, we will continue to see metastatic thyroid carcinoma. The incidence of bone metastasis from carcinoma of the thyroid varies widely in different clinics. Abrams[3] analyzed metastases in 1,000 consecutive cases of malignant neoplasms of epithelial origin autopsied at the Montefiore Hospital between 1943 and 1947. In every instance, gross and microscopic studies of bone for metastasis were undertaken. Of the 1,000 cases, there were 10 carcinomatous thyroids, 5 of which showed bone metastases, an incidence of 50 per cent. He also summarized the incidence of skeletal metastases at autopsy from the literature and found 1,585 cases of carcinoma of the thyroid, 303 of these showed bone metastases, an incidence of 19 per cent. Outerbridge[4] reports that of 2,268 thyroidectomies done at the Toronto General Hospital over a 20 year period, 60 (2.6 per cent) were done for carcinoma of the thyroid. Of these, 24 were diagnosed as adenocarcinoma or malignant adenoma of the thyroid. Five of these malignant adenomas had metastasized to bone, an incidence of 20.8 per cent.

Metastatic bone lesions from the carcinomatous thyroid are osteolytic lesions, and frequently are of considerable size before detection. (Coley[5] states that the lesion frequently resembles an osteogenic sarcoma of the osteolytic type or an aggressive giant cell tumor.) The most common sites of metastasis are skull, vertebra, pelvis, clavicle, sternum, femur, rib, humerus, scapula and mandible.[6] When it appears in the long bones, the growth is near the epiphysis. There is frequently a lapse of several years after thyroidectomy before bone metastasis may be detected. However, once bone metastases are detected, the disease is usually fatal within about two years.[7] Nevertheless, there are reported exceptions to this conclusion. Coley[5] mentions a patient in which a metastasis to the ilium, first observed 13 years after thyroidectomy, was treated by irradiation and is still alive 8 years post-treatment. Roswitt[8] mentions a case "cured" by radioactive iodine treatment, but details of the case are not known.

The conventional treatment of carcinoma of the thyroid with bone metastasis is: (1) eradicate the primary site, then (2) eradicate

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†From the Miller Clinic, Charlotte, N. C., and Shriners Hospital, St. Louis, Mo.

the metastatic lesions by radical surgery, if possible, or (3) use irradiation alone, or in combination with surgery. Since the advent of radioactive iodine, some patients have been given several more years of life, but this form of treatment is still applicable in only a few cases. Less than 15 per cent of metastatic tumors will pick up radioactive iodine. These are the ones showing a well-differentiated, follicular, colloid-forming structure. Before these can be stimulated to pick up therapeutically effective dosages, all normal thyroid tissue must be ablated. This latter is preferably done by surgery, but in some cases can be accomplished by the use of radioactive iodine. Even after total ablation of non-neoplastic thyroid, thyroid stimulating hormone must be given in some instances to induce the metastasis to pick up a therapeutically effective amount of radioactive iodine. In using radioactive iodine, its toxic effects, especially on the hematopoietic and renal systems, must be kept in mind.[9,10] Seidlin and associates[11] report a six-year follow-up on 12 cases in which radioactive iodine was used, 7 of the group are living; 3 greatly improved; 2 moderately improved; and 2 in a stationary condition. Of the 5 who died, 3 showed temporary improvement immediately after treatment was begun. Sorrentino, Roswitt, and Yalow[8] report an interesting case treated with radioactive iodine, almost moribund at the beginning of treatment. Under treatment a pathologic fracture of the spine and of the scapula united. Other metastatic lesions seemed to have been arrested, and the patient is clinically well. In this case, evidence of toxicity in the hematopoietic system as well as a mild degree of renal tubular damage was demonstrated, supplementing the literature on this subject to a small degree.

We wish to report a case of our own in which a metastatic lesion was followed for 16 years. The metastasis was detected one year after thyroidectomy but a conclusive diagnosis could not be substantiated at that time, as the patient refused to submit to biopsy. Sixteen years later, because of the size of the lesion and associated pain, the patient submitted to operation and the diagnosis was confirmed.

Case Report

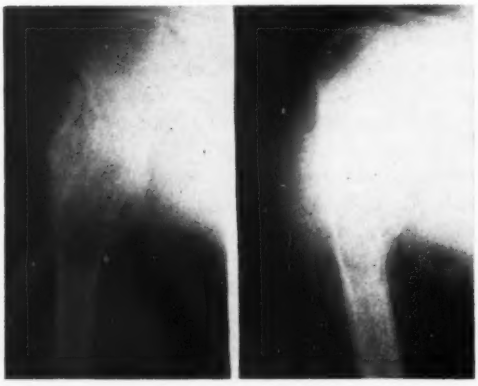
C. A., a white man, first noted an enlargement in his neck in 1929, at the age of 24. This gradually increased in size until 1937 when it was larger than a grapefruit. For several years he had symptoms of toxicity manifested by nervousness and loss of weight (20 lbs.). In 1937, a thyroidectomy was done and the surgeon's note contained the following description: "Very large cystic growth, size of grapefruit, substernal and retrotracheal."

The pathological report read as follows: "The specimen consists of a piece of thyroid tissue measuring 9 by 8 by 2 cm. The tissue is largely occupied by cysts in which there is considerable granular brownish material. The remaining thyroid tissue shows numerous small circumscribed nodular areas. Microscopically, there are numerous small alveoli, only a few of which contain colloid, which are lined by columnar epithelial cells. There is considerable interstitial hemorrhage. Diagnosis: Cystadenoma."

The postoperative course was uneventful. The man regained his former weight and was not nervous, thereafter.

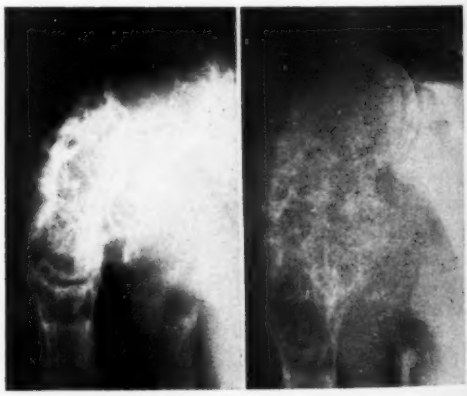
The patient returned to work and did well until

FIG. 1



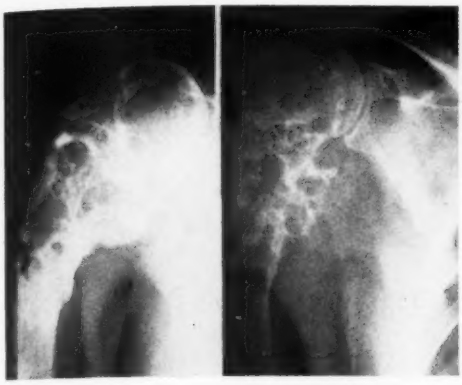
Feb. 29, 1941

FIG. 2



A. Aug. 31, 1942 B. Aug. 11, 1943

FIG. 3



A. June 10, 1944 B. Feb. 28, 1946

March, 1938. At this time, while he was using a drill, which required his whole body force, the bit suddenly sank through the steel beam he was drilling. The man had immediate pain in his right upper arm and x-ray examinations revealed a pathologic fracture in the upper third of the humerus. The fracture was treated by means of a hanging cast. After the fracture healed, he returned to work and did well, except for an occasional twinge of pain at the old site of fracture.

In December, 1939, patient started to fall from a sawhorse and used his right arm to brace himself, preventing the fall. Shortly, he noted pain and swelling in the upper third of the right humerus which was soon followed by some discoloration of the skin. X-ray films revealed a fracture through an osteolytic lesion in the upper third of the right humerus. The films of March, 1938, were then reviewed and revealed early evidence of osteolytic changes which had been overlooked previously. At the conclusion of another period of treatment for injury to the arm, he returned to work as a carpenter, but was always aware of some weakness in his right arm. In November, 1940, while using a handsaw, he noted pain in his right upper arm following a sudden jerk, when the saw stuck temporarily. X-ray films again revealed a fracture through the cystic areas of the previously noted lesion.

This patient was first seen in our clinic in February, 1941, because of pain and limitation of motion of the right shoulder. The lesion was at once noted on x-ray examination (Fig. 1), and he was advised to have a biopsy. It was felt that this was most likely a giant cell tumor. He refused operation at that time since he was able to carry on his work without any major handicap. Following his last fracture referred to, the man quit carpentry and began working as a guard which required no manual work. He did, however, continue to have pain in his arm and noted a definite weakness in it. He also felt that the arm was increasing in size near the shoulder. His course was followed regularly until 1942, with increasing pain and size of the right upper arm. Since he continued to refuse operation, irradiation was proposed (Fig. 2).

FIG. 4

Feb. 9, 1954

He went to a V. A. Hospital where irradiation therapy was given to the arm. In October, 1942, he received 3,400 roentgen units to the arm and because of the improvement, in October, 1943, he was given an additional 1,800 roentgen units.

For about two years following the irradiation therapy, the patient was free of pain and the arm felt much stronger. However, there was never any decrease in the size of the tumor, nor was there any increase in range of motion (Fig. 3). In 1945, the pain recurred and the arm began steadily to increase in size. This did not prevent him from carrying out his

FIG. 5

Dec. 1, 1954

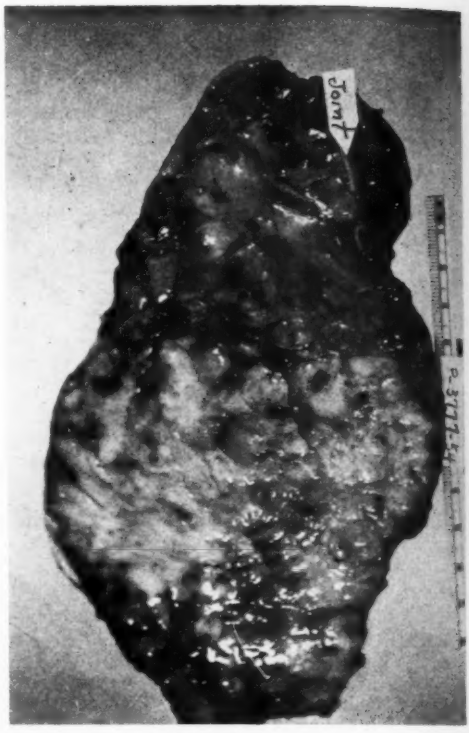
duties as a guard, however, so he continued to refuse surgery. In September, 1952, at a V. A. Hospital, a needle biopsy was obtained and the microscopic examination revealed only blood and fibrin. In early 1954, (Fig. 4) the patient noted that the pain became worse and almost constant. In addition, the arm was now rapidly increasing in size. Because of this, in December, 1954, (Fig. 5) he agreed to operation and was admitted to the hospital. It was felt that a forequarter amputation must be the treatment of choice because of the chronicity, the increasing size of the mass, previous irradiation and proximity to the shoulder joint.

Physical examination revealed a well-developed, well-nourished white man in a depressed state. Positive findings were limited to the neck and right upper extremity. *Neck:* There was a good range of motion of the cervical spine without tenderness on motion or palpation. There was a well-healed thyroidectomy scar. Both lobes of the thyroid were palpable and felt to be about normal in size. There was no thickness or induration in the neck. *Right Upper Extremity:* There was marked swelling and induration of the right shoulder extending from the middle third of the arm into the pectoralis muscles anteriorly and the spinatus muscles posteriorly. It was estimated that the shoulder and upper arm was about twice normal size.

FIG. 6

Gross specimen

FIG. 7



Cut section of gross specimen.

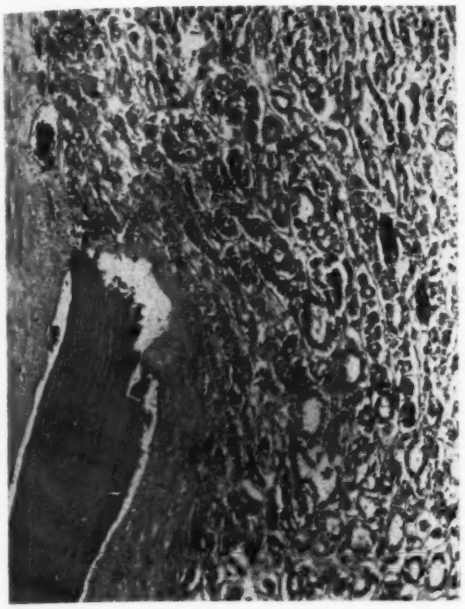
The overlying skin was red, tender, and stretched thin. The mass was firm and tender to palpation. No bruit or pulsation could be felt. There was some swelling in the forearm; however, the pulses were only slightly diminished and there was normal sensation. There was no impairment of the motion of the elbow or hand. Chest was clear to percussion and auscultation.

Laboratory Studies: Hemoglobin 92 per cent; RBC 4.68 million; WBC 9,450; differential, normal. Urine was clear; specific gravity, 1.008; albumin negative; sugar three plus. Microscopic, occasional epithelial cells. Serum calcium, phosphorus, and acid and alkaline phosphatase determinations were within normal limits. X-ray films of the skull, chest, lungs, vertebrae, and pelvis were negative for any other metastases. Our tentative diagnosis then was malignant giant cell tumor or chondrosarcoma.

Because of the glycosuria, a fasting blood sugar was done and discovered to be elevated. He was found to be a mild diabetic requiring both diet and insulin while in the hospital. (Since discharge from the hospital, he has required 10 units of NPH each morning until two months ago and is now insulin free but remains on a diet. There was no family history of diabetes and he had had no previous symptoms indicating a diabetic condition.)

At operation, a forequarter amputation was done

FIG. 8



Microscopic section

using a racket incision. When the pectoralis muscles were cut, there was considerable induration but no evidence of tumor tissue. The scapular muscles, when incised, appeared normal. The patient received three pints of blood on the table and withstood the operation well. His postoperative course was uneventful; the wound healing per primum without any complications.

The *pathological report* was as follows:

Gross: "The specimen consists of an entire right arm with the scapula and major portion of clavicle attached. The proximal half of the upper arm is markedly expanded by a palpable tumor mass. The tumor, which completely encircles the upper half of the humerus, is dissected en bloc with the humerus. The mass measures 17.5 by 11 by 7.5 cm., and is partially encapsulated, pushing soft tissue structures ahead of it. In particular, the major arteries, veins, and nerves circumvent the tumor. Small unencapsulated areas infiltrate adjacent skeletal muscle. The cut surface of the tumor is somewhat lobulated, and partially composed of yellowish, quite moist grayish tissue which is focally yellowish or hemorrhagic tissue. It has essentially destroyed the upper segment of the shaft of the humerus, where only an infrequent residual spicule of bone can be discovered. The major portion of the cartilaginous joint surface at the shoulder joint has been spared. The adjacent lower segment of humerus is attached merely by soft tumorous tissue and periostium reflected over the surface of the tumor. Portions of the soft tissue capsule of the shoulder joint are infiltrated, but the glenoid fossa of the scapula is spared (Figs. 6 and 7).

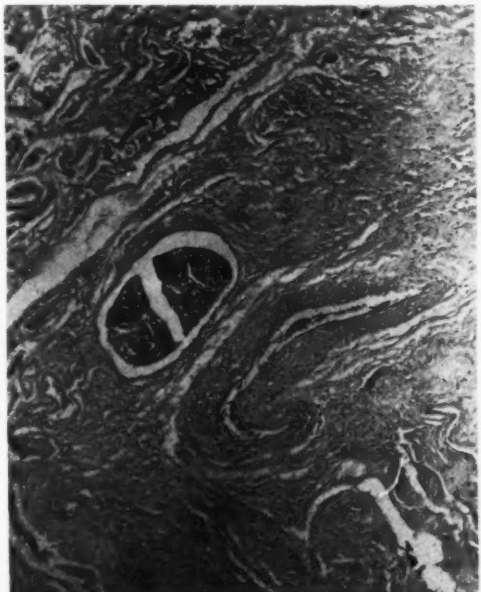
Microscopic: "The tumor is a well-differentiated adenomatous one composed of innumerable acini which for the most part are relatively small. They are lined with low columnar and cuboidal epithelial cells which are fairly uniform in shape, size and tinctorial quality, not only of cytoplasm but of nuclei as well. Everywhere, in many sections, well-differentiated gland spaces are observed, and in many areas variable quantities of eosinophilic colloid substance is observed within acini. Infrequently, a few small groups of epithelial cells are arranged in short fascicles. At the perimeter of the tumor, the latter is seen to infiltrate adjacent connective tissue capsule, skeletal muscle, and furthermore, infrequently groups of tumor cells are observed within the lumina of veins. The adjacent bone shows marked osteoclastic rarefaction unattended by significant osteoblastic apposition" (Figs. 8 and 9).

Interpretation: "Metastatic well-differentiated acinar adenocarcinoma of thyroid in bone. The tumor infiltrates the immediate soft tissues and muscles. Although essentially the entire upper portion of the humerus has been destroyed, the tumor does not extend into the clavicle."

Summary

We have reported a case of solitary thyroid metastasis to a single bone (upper humerus) known to have been present for 16 years. The final diagnosis was substantiated by microscopic sections.

FIG. 9



Microscopic section showing tumor cells in lumina of vein.

A forequarter amputation has allowed the patient to wear a prosthesis and return to work free of pain. It is now 18 years since thyroidectomy.

We are indebted to Dr. Lee Large, Presbyterian Hospital, Charlotte, N. C., for his help on the pathologic interpretation.

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Discussion (Abstract)

Dr. Thomas O. Shindler, Houston, Tex. I would like to say first of all that we certainly have enjoyed this interesting paper, particularly for those of us on the Gulf Coast who very rarely have occasion to see metastatic thyroid carcinoma. Most of the primary lesions, as you know, with radioactive medications are treated by the internist, but once in a while we do see metastatic lesions from the thyroid, and I think in the Hermann Conference over the last five years we have seen perhaps two or three.

It is certainly remarkable that an individual could survive this type of thing for 16 years, and it is evident that we know so little or yet have much to learn about the behavior of malignant cells.

When Dr. John Goode of Dallas was here to address the Houston Surgical Society some time ago, he likened the behavior of malignant cells to infecting organisms. For example, he mentioned the streptococcus as one situation. And in this particular case, too, of course, there is much for us to learn about behavior of the organisms. I recall that one paper was presented in the *Journal of Bone and Joint Surgery* some months ago in regard to 80 years elapsing between the original osteomyelitic infection and its exacerbation, truly an unusual and rare situation as this unusual cellular behavior is.

In reading the original paper Dr. Conners mailed to me, he said that they had considered, I believe, primary chondrosarcoma just before surgery. I just wondered if they did this on the basis of the lapse of time between the thyroidectomy and the time of operation and also because there were no other lesions. For an individual to have a malignancy the size of this one and have no pulmonary lesions was a thing I should think I would never see again. The complete radiologic survey was negative.

As noted above, those of us in this area see very few cases of thyroid carcinoma, and certainly fewer metastatic ones. For the last three years, out of over 78,000 cases discharged from Hermann Hospital, 132 were diagnosed as thyroid carcinoma or an incidence of 0.17 per cent of all the cases. I do not know what this means, whether they all come to the hospital or what, but it seems to me that in the over-all picture it is fairly rare.

One thing about the management of metastatic bone lesions, I think they should be treated when there is a pathologic fracture like any other fracture. Certainly, I think almost everyone agrees with that, whether it be treated by external immobilization such as plaster, or whether it be treated, in addition to the radioactive methods that we have now, by excision of the metastatic lesion if we believe that the original lesion has been completely removed. All of these things I think should be kept in mind.

It has been my impression, though I have seen more metastatic breast lesions, that when metastases occur, they also are metastatic in the lung and perhaps in the brain which makes it pretty hopeless.

I think of nothing else to add to this paper. I would like to say that we are indebted to the authors for giving us this very unusual case.

Tuberculosis and Pregnancy*

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Memphis, Tenn.

With the recent advances in the management of tuberculosis the attitude toward pregnancy in the tuberculous patient has been changed. It appears that therapeutic abortion is not indicated under good circumstances and that pregnancies may be planned with safety.

ALTHOUGH THE INCIDENCE OF THERAPEUTIC ABORTION in tuberculous patients has been declining in recent years, there is still much apprehension in the attitudes of many obstetricians and internists concerning the effects of pregnancy on pulmonary tuberculosis and, to a much lesser degree, the reciprocal effects of tuberculosis on the pregnancy.

Nearly fifty years ago, J. Whitridge Williams,[1] famed obstetrician of the Johns Hopkins Hospital, wrote concerning tuberculosis in pregnancy, "It is the duty of the physician to induce abortion—I feel very strongly that interference is not only justified but almost imperative." Some years later, after further evaluation of the problem and consideration of the results of therapeutic abortion, he modified his views and wrote, "While I am no longer a radical interventionist, I regard the occurrence of pregnancy in women with tuberculosis as a great misfortune, and consequently I recommend the prevention of pregnancy by the most available contraceptive methods." Since that time a voluminous literature has accumulated. In it there is extreme variation of opinion regarding the subject of pregnancy and tuberculosis.

There is a paucity of large groups of these patients reported in the literature, and therefore statistically significant data are not as easily available as with many other disease entities. One of the most recent reports by Hedvall,[2] in 1953, analyzed the results of 346 pregnancies in patients with pulmonary tuberculosis. His results revealed that during pregnancy the status of the tuberculosis remained stationary in 83.9 per cent of patients, was improved in 9.1 per cent, and deteriorated in 7 per cent. During the first postpartum year the tuberculosis was stationary in 76 per cent, improved in 8.8 per cent, and deteriorated in 15.2 per cent. The deterioration was attributed by Hedvall to the over-all tendency of the tuberculous process to progress spontaneously, demonstrable also in nonpregnant patients, and he feels the prognosis is approximately the same in pregnant and nonpregnant groups.

As to therapeutic abortion, Hedvall believes that the advent of improved and specific chemo-antibiotic therapy has drastically reduced the indications for this procedure. Schaefer and Epstein[3] have compared groups of tuberculous patients who were therapeutically aborted with groups allowed to proceed to term and deliver. They suggest also that the recent advances in the medical and surgical treatment of tuberculosis, together with the decline in maternal mortality from 60 per 100,000 in 1932 to 10 per 100,000 in 1950 render the older statistics obsolete and suggest a revision of our previous teaching relative to combined pregnancy and tuberculosis. Schaefer and Epstein also noted that 30 per cent of the patients with far advanced disease died or progressed after therapeutic abortion, while only 14 per cent with far advanced lesions died or progressed when the pregnancy was allowed to go to term and active treatment instituted during the antepartum period. They feel, therefore, that the prognosis is most influenced by the type and extent of the disease and by the institution of early and adequate treatment.

Materials and Methods

During the period 1949 to 1954 inclusive, there were 92 obstetrical patients admitted to the West Tennessee Tuberculosis Hospital. In this group there were 80 deliveries (55 of which were followed by immediate postpartum sterilization) and 12 therapeutic abortions. Also 9 elective sterilizations were per-

*Read before the Section on Obstetrics, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

†From the Division of Obstetrics and Gynecology, University of Tennessee College of Medicine and the West Tennessee Tuberculosis Hospital, Memphis, Tenn.

TABLE 1

EXTENT OF DISEASE AMONG 80 TUBERCULOUS, PREGNANT PATIENTS

Admission Diagnosis	*Number*	*Per Cent*
Pleurisy with effusion	3	3.7
Minimal	17	21.3
Moderately advanced	18	22.5
Far advanced	42	52.5
Total	80	100.0

formed. These were not associated with delivery, and therefore, were not included as "obstetrical" cases.

Of the 92 pregnant patients, the mean age was 25.2 years. In the 80 patients delivered 61 (or 76.2 per cent) were multiparas and 19 (or 23.8 per cent) were primiparas; 46 (or 57.5 per cent) were colored and 34 (or 42.5 per cent) were white. The records of these patients were reviewed from the obstetrical viewpoint and also carefully studied to see what changes, if any, occurred in the course of their pulmonary disease. The clinical management of the tuberculosis was under the direction of the Staff of the West Tennessee Tuberculosis Hospital, and the obstetrical care was provided by the Staff of the Division of Obstetrics and Gynecology of the University of Tennessee College of Medicine.

Classification of the pulmonary tuberculosis in the 80 pregnant patients delivered is outlined in table 1.

This table reveals that their tuberculosis was preponderantly beyond the stage of minimal disease and corresponds with the extent of tuberculosis among sanatorium admissions in general. The fact that more than half had far advanced disease may be related to a preponderance of colored patients (57.5 per cent).

During the prenatal period, there were six complications, one each of: acute cystitis; pyelitis; nonresponsive iron deficiency anemia; mild preeclampsia; and severe preeclampsia. One patient was Rh negative but her infant showed no signs of incompatibility. This compares favorably with the incidence of complications among unselected patients of the same age.

TABLE 2

METHODS OF DELIVERY

Method	*Number*	*Per Cent*
Spontaneous	48	60.0
Low forceps	24	30.0
Mid forceps	1	1.2
Cesarean section	7	8.8
Total	80	100.0

TABLE 3

ANESTHESIA

Type	*Number*	*Per Cent*
General inhalation	42	52.3
Spinal (saddle block)	14	17.6
Caudal	3	3.7
None	21	26.4
Total	80	100.0

With few exceptions all patients were allowed to go into labor spontaneously, and the average length of labor was 4 hours and 39 minutes. The types of delivery are shown in table 2, and anesthesia in table 3.

Complications or abnormalities of labor and delivery did not appear to be significantly different from the usual in their incidence and are listed in table 4. Prophylactic episiotomies were performed on 20 patients (25 per cent).

Puerperal obstetrical complications involved three patients with a morbidity of 3.8 per cent. There was one case of endometritis, one infected episiotomy wound, and one wound infection following cesarean section. There was one late complication, a rectovaginal fistula following a previously infected episiotomy.

Finally, a careful analysis was made of any clinical and radiologic evidence of change of status of the pulmonary disease and these results are summarized in tables 5 and 6.

The patients were observed in the hospital for an average of 14.5 weeks antepartum and 22.3 weeks postpartum, as of January 1, 1955. No attempt has been made to include follow-up information after discharge because we were primarily interested in the course of

TABLE 4

INTRAPARTUM COMPLICATIONS

	Number	*Per Cent*
Premature delivery	3	3.8
Forceps rotations	2	2.5
Breech delivery	1	1.2
Twins	1	1.2
Placenta previa	1	1.2
Manual removal of placenta	3	3.8
Cervical lacerations	1	1.2
Perineal lacerations	6	7.5
Induction (preeclampsia)	1	1.2
Total	19	23.6

TABLE 5

STATUS OF TUBERCULOSIS PRIOR TO DELIVERY

	Number	*Per Cent*
Stable	32	40.0
Improved	46	57.5
Worse	2	2.5
Total	80	100.0

the patient during the observed portion of the pregnancy and in the early weeks and months following delivery, while the patient was under the close observation that is possible only during hospitalization. After the patient leaves the hospital the important factors of the environment vary greatly and are not well known.

The term "stable" used in tables 5 and 6 represents a favorable situation in most cases. The important point is that the tuberculosis became worse in only two cases during the pregnancy and in only three patients following delivery. The two cases growing worse before delivery were also among the three showing progression of their disease after delivery.

Although no therapeutic abortion has been performed since 1952, the 12 cases prior to that year were reviewed. This small series was not comparable with the entire group of pregnant tuberculous patients inasmuch as all of these patients had tuberculosis of long duration, and in only one patient was the disease active on admission. Most of them had had previous periods of hospitalization. All had been treated prior to the onset of the pregnancy and many had undergone extensive surgery. The chest x-rays showed stable lesions, and in no case did sudden change occur during the few weeks of pregnancy or following abortion.

Discussion

Whatever one's views regarding the relative hazards of pregnancy in the tuberculous patient, probably all will agree that there are

TABLE 6

STATUS OF TUBERCULOSIS FOLLOWING DELIVERY

	Number	*Per Cent*
Stable	47	58.8
Improved	30	37.4
Worse	3	3.8
Total	80	100.0

circumstances connected with childbearing and family care, which do have adverse influence on the course of tuberculosis. These include increased physical exertion, nutritional demands and disturbances, disturbed rest, and worry connected with the care of the young children. These undeniable factors of stress occur even in families of comfortable financial circumstances. Among the low income families, they often are of an extreme importance; therefore, prevention of a further increase in the family size is often indicated. Tubal ligation appears to be the most certain practical way of preventing later pregnancy. This decision must, of course, be carefully arrived at for each individual. One must consider the extent, duration, and behavior of the tuberculosis in that person, the age and number of children, the income and intelligence of the family, the personal principles and wishes of the husband and wife, the patient's age and marital status, and the prognosis for the particular individual.

Therapeutic Abortions. The fact that no therapeutic abortion has been performed in our hospital since 1952 reflects the belief that almost every tuberculous pregnant woman can be carried to term and delivered without increased danger to her. The sharp cessation of therapeutic abortions in late 1952 coincided with the better prognosis for the tuberculous patient as a result of the use of potent antibiotics and resectional therapy.

In spite of this, we should not say that there is never a need for therapeutic abortion in these patients. For instance, there is the case of a woman who has had bilateral tuberculosis for several years. As a result of this long-standing widespread disease, though she is comfortable at rest, the slightest exertion or an acute respiratory infection plunges her into dyspnea and cyanosis. She could not carry a fetus to the point of viability. To try to do so would result in death of the fetus and the patient.

Planned Parenthood. All of us are quite familiar with the patient who asks the doctor's advice and, having received a carefully considered reply, is quite content to do what she wanted to do in the first place. This seems to be particularly true in the case of the young woman with tuberculosis who has a marriage proposal. There are, however, some young married couples who can and will postpone the rearing of a family until the

prospective mother seems to have safely recovered from her tuberculosis. This raises the question of when such a patient may plan a pregnancy. Suggested general rules[4] are as follows:

1. With minimal tuberculosis treated, allow two years of observation after arrest of the disease before pregnancy.

2. In moderately advanced tuberculosis, wait three years after arrest of the disease before pregnancy.

3. In far advanced tuberculosis, wait five years after arrest of the disease.

Such a scheme provides a basis of planning which can be altered to fit the specific case. In general, it seems that the period of contraception should be in terms of the period of inactive disease and that the contraceptive periods might be somewhat shortened from the above schedule. For instance, the young woman who had a minimal unilateral lesion which disappeared on x-ray examination, or quickly became a small fibrous scar with today's antibiotics, may be quite safe in a pregnancy, beginning a year after her disease was considered inactive. Likewise, a woman who has no demonstrable residual tuberculosis after pulmonary resection for well-localized, unilateral, moderately advanced tuberculosis may quite safely go through pregnancy at an earlier date than indicated in the above scheme.

Labor. In the past, much has been said about the "strain of labor" as a factor in causing exacerbation of tuberculosis in the postpartum period. If this were very important, one would expect to see x-ray evidence of increased disease and other signs of a worsening condition in the examinations following soon after the termination of the pregnancy. Actually only three of the 80 patients became worse in this period. One developed tuberculous meningitis which actually had its beginnings a few days prior to delivery. She recovered on appropriate chemotherapy. Another had fulminating, far advanced, bilateral, pulmonary tuberculosis throughout the observed prenatal period and died a few weeks after delivery. A third individual with far advanced, pulmonary tuberculosis was admitted during the seventeenth week of gestation. Throughout the period prior to delivery her sputum remained positive, her general condition was poor, and there was only questionable improvement in serial chest x-ray films. Six weeks following cesarean section, the chest film showed slight worsening of her tuberculosis. Chemotherapy was not used until after the cesarean section, and thereafter her condition was unchanged until the right upper lobe was removed six months later. She was finally discharged with arrested tuberculosis. The unfavorable postpartum course of these three women is no more than one would have expected in a similar group of nonpregnant tuberculous patients.

Anesthesia. Often there is the question of what anesthetic to use. Usually, the obstetrician may disregard the tuberculosis and use the anesthetic he would ordinarily prefer. In the event that the patient has copious sputum and there is danger of bronchial dissemination of the tuberculosis or obstruction of the airway during the anesthesia, inhalation anesthesia is preferred. This is true because tracheal aspiration can be done readily. Also, inhalation anesthesia is preferred in instances of pulmonary insufficiency. Tracheal intubation may be necessary. By these means, the airway can be kept clear of mucus and adequate oxygen and ventilation can be assured.

The Baby. Although tuberculous infection of the fetus in utero has been known to occur,[5] this happens so rarely in the case of viable infants that one can in practice ignore the problem of congenital tuberculosis. In sharp contrast is the very serious danger of exposure of the infant. For this reason, strict, immediate isolation from the mother who has active tuberculosis is necessary. Likewise, the tuberculous mother should never breast-feed the baby. Not to be overlooked is the worry and broken sleep associated with the care of the infant. For the mother's sake, arrangements should be made for someone else to assume this burden until the mother's tuberculosis is inactive. This is often difficult and plans should be well thought out far in advance of the completion of the pregnancy.

Treatment of the Tuberculosis. Active treatment of the tuberculosis including rest, chemotherapy, collapse measures, and even surgical therapy can be safely done during the first two trimesters of the pregnancy. Usually in cases of frankly active tuberculosis major thoracic surgery is postponed until after delivery. Rest, chemotherapy, and reversible collapse measures may be continued

throughout the pregnancy. Antituberculous drug toxicity is not a problem in the fetus or newborn.

Summary

1. Pregnancy and delivery cause no significant deleterious effect on the hospitalized patient with pulmonary tuberculosis.

2. It is felt that the increased activity incident to family care *does* adversely affect the disease.

3. Careful use of "planned parenthood" technics according to previously suggested rules, although ideal, is often not adhered to by patients.

4. Sterilization by tubal ligation is the most effective means of limiting family size.

5. Spontaneous labor should be encouraged, cesarean section being reserved only for obstetrical indications.

6. Therapeutic abortion is almost never indicated in the tuberculous patient.

7. The obstetrician may use whatever anesthetic he ordinarily prefers, unless the patient has copious sputum or low pulmonary reserve. In these instances, general anesthesia, occasionally with tracheal intubation, is preferred in order to maintain a clear airway and to assure adequate oxygenation.

8. The infant should be separated from mother after birth to prevent infection by contagion and to relieve the mother of the strain of its care.

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Discussion (Abstract)

Dr. Herman I. Kantor, Dallas, Tex. In discussing any paper, a basic rule which all good discussers feel compelled to follow is to find some points in the paper with which they might disagree. After reading and hearing this excellent paper by Drs. Bowerman and Everett, I was hard pressed to find such areas of disagreement, especially in the major premises which they made.

However, I finally found a point on which I should like to place myself on the opposite side of the fence. I firmly believe that inhalation anesthesia is best avoided in any type of respiratory ailment, and especially in pulmonary tuberculosis during the active phase. We believe that local infiltration or regional block are the desirable anesthetic methods for this group of patients. The cough reflex remains unimpaired and respiratory irritants are thereby avoided.

I would like to ask about the incidence of cesarean section of 8.8 per cent. Were some of these performed for purely obstetric indications?

I would also like to ask the authors about their analgesic medications during labor in the patient with tuberculosis. Is it different from the routine they usually follow?

Our study of tuberculosis and pregnancy in Dallas was tabulated along lines similar to those indicated by the authors.

When the patient who has healed or arrested pulmonary tuberculosis is permitted to have a planned pregnancy, it somehow represents a true therapeutic triumph. It is a tribute to the success of our modern attack on this disease, and the newer chemotherapeutic drugs have contributed greatly to this success.

On the other hand, the diagnosis of pregnancy in a woman in whom tuberculosis is not under control, or in whom the disease was not even suspected, may mean a hazardous and frustrating complication. The effects of pregnancy on pulmonary tuberculosis must, of necessity, be considered from these two viewpoints:

a. The planned pregnancy in the arrested disease.

b. The unsuspected pregnancy in the active disease.

The following tables from two hospitals (Table 1) reflect our experience in Dallas from January, 1950, through December, 1954, five years. Baylor Hospital is essentially a private institution with a small charity service. Parkland Hospital serves the indigent population of Dallas City and County.

Table 2 reveals a significant difference in the incidence of pregnancy complicating tuberculosis at these two institutions. However, from the description of the hospitals, the factors responsible for this difference become obvious. It may also be pointed out that patients with communicable diseases are sent to the

TABLE 1

TUBERCULOSIS IN PREGNANCY 1950 THROUGH 1954

Baylor Hospital	9	Private Hospital
Parkland Hospital	33	City-County Hospital

TABLE 2

Hospital	*Deliveries*	*Tuberculosis*	*Incidence*
Baylor	24,104	9	1: 2,678
Parkland	13,665	33	1: 414

TABLE 3

TUBERCULOSIS BEFORE PREGNANCY

Hospital	*Known*	*Unknown*
Baylor (9)	8	1
Parkland (33)	23	10

TABLE 4

METHOD OF DELIVERY

Hospital	Pregnancy Interrupted	Vaginal	Cesarean Section	Sterilized
Baylor (9)	4	2	3*	2
Parkland (33)	1	32	0	3

*1 for obstetrical indication.

City-County institution, where isolation wards have been established.

Table 3 indicates that an unanticipated and unplanned pregnancy is more prone to occur among the indigent population.

Table 4 demonstrates that the more extensive experience at Parkland supports the safety of vaginal delivery. With the exception of uncontrolled and fairly severe tuberculosis, it is preferable to permit the pregnancy to progress to term, and then to deliver vaginally if obstetrically possible.

The method of anesthesia in relation to the status of the tuberculosis is shown in table 5. Again, with the larger experience at Parkland Hospital, regional or local anesthesia is preferred. In a few patients Trilene has been used, and when the mother cooperates well it has proved to be fairly successful.

The patients not included in this chart were those who were encouraged to use vocal expressions of their resentment to the labor contractions. They were usually multipara who delivered before any anesthetic could be administered.

Table 6, the effects of pregnancy on tuberculosis, proved difficult to evaluate. Even when no ill effects were described in the charts, they may well have appeared after discharge from the hospital. The entire puerperium is still a period of danger, during which the tuberculosis must be carefully watched. However, in only five of the entire group was the tuberculosis described as aggravated, and one patient died during her puerperium. All of these five patients had active and uncontrolled disease which was further complicated by the unplanned pregnancy.

In conclusion, our present medical, chemotherapeutic and surgical attack on tuberculosis has made great strides. No longer may these patients be categorically denied the pleasures of a family. However, such pregnancies must be carefully planned in order not to relight or aggravate the pulmonary disease. Vaginal delivery at term using regional block or local infiltration anesthesia, is the preferred regimen. In general, it would still seem medically, socially and economically wise to restrict the size of the families of women who have had pulmonary tuberculosis.

TABLE 5

Hospital	Anesthesia Local	Reg.	General	Status of Tuberculosis Active	Arrested
Baylor (9)	1	1	7	5	4
Parkland (33)	10	12	0	23	10

TABLE 6

EFFECTS OF PREGNANCY ON TUBERCULOSIS

Hospital	Unknown	None Described	Aggravated
Baylor (9)		8	1*
Parkland (33)	12	17	4*

*Active disease not controlled during pregnancy.

Dr. Walter L. Thomas, Durham, N. C. The essayists have given us a great amount of information which should prove very helpful to medical men as well as to the obstetricians. They have clearly shown that the new antibiotics and the resectional surgery have changed the entire picture of pulmonary tuberculosis during the past few years. However, I would point out that the patients reported in this series were *in a sanatorium for three months on an average before delivery and for six months after delivery.* They were receiving the very best of care possible.

We are not so fortunate in North Carolina. We occasionally have to handle these patients in a general hospital for a variety of reasons. There are some patients who cannot get into the sanatorium; others refuse to go to the sanatorium. We simply do not have the same ideal conditions as the fine set-up in Memphis. The economic situation, the home situation, and many other factors play a role which tax us at times in deciding what is best for the individual under many adverse circumstances.

Another thing, planned parenthood in North Carolina does not work too well. Permit me to cite this example. We had a 22 year old white para 1-0-1 who spent two months in our hospital while nonpregnant. She had been very ill with tuberculous meningitis and unilateral pulmonary tuberculosis. She was discharged home. Before her discharge the patient was fitted with a vaginal diaphragm and told of the importance of not getting pregnant. Within four months she returned and was found to be seven weeks pregnant. We asked her whether she used the diaphragm. She replied, "I used it for the first month, then my husband found it was so effective that he started using it on his girl friend." So planned parenthood, at least in a lot of instances, does not work too well. Every patient is an individual problem. No general rule can be laid down that applies to all. Occasionally there might be an indication for a therapeutic abortion, but never after the first trimester.

Now, a statement about general anesthesia for delivery. I agree that the general anesthesia in such a well-equipped hospital or sanatorium might be perfectly all right if it is given by a highly trained anesthetist who is very expert in pulmonary procedures. Certainly that trained anesthetist will keep the patient well aspirated. However, I am extremely doubtful of general anesthesia for these patients in most hospitals. Some type of regional anesthesia such as paravertebral block, pudendal block, saddle block, and so forth, should be used. In my opinion, local or regional block would be far safer. Each patient in each particular hospital is an individual problem and must be so managed.

I agree that this infant must be protected following the delivery. This seems to be a big problem also in North Carolina.

At the present time, we have no hospital or place

to put these infants; at least our state does not provide such a place, and at times it seems impossible for us to work this out with the family before delivery or even after delivery.

Finally, we still feel that for sterilization purposes, a total hysterectomy, and preferably the vaginal approach, is far better than ligation of the tubes. The tubal ligation for sterilization has failures. With the hysterectomy there are no failures. Also there is no opportunity for benign or malignant disease to develop in an organ whose sole function is to serve as a nidation for the fertilized ovum, to carry it to maturity and to expel it. A woman's future health is more secure by such a procedure.

It has been a pleasure to discuss this paper.

Dr. Bowerman (Closing). Thank you both, Dr. Kantor and Dr. Thomas.

I am not sure that I can answer the entire question about the cesarean sections. I do know that one patient had a placenta previa. Another one had had a previous section with an earlier pregnancy. I think also the factor of our changing concepts concerning the handling of these patients came into play during this period.

I do not believe that I have anything further to say about the anesthesia. I do not think that it is often of critical importance and usually is carried out satisfactorily in accordance with the particular preferences of the obstetrician and anesthetist.

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The Use of Cobalt and Iron in the Prevention of Anemia of Pregnancy*

HUGH G. HAMILTON, M.D., *Kansas City, Mo.*

The author, in his belief that the toxicity of cobalt has been overemphasized, continues his studies in the treatment of anemia in pregnancy with this metal as a supplement to iron.

IN RECENT YEARS SUFFICIENT PROGRESS has been made in studies of anemia in pregnancy that it is generally accepted that the regularly appearing anemia seen is one due to iron deficiency. That there is an increase in fluid volume of blood is clearly understood, but if the bone marrow does not keep pace with the rise in blood volume, except in rare instances, the problem is essentially that of insufficient iron supply reaching the bone marrow. The concept of a "physiological" anemia of pregnancy is sufficiently well interred (with due ceremony) that the term is commencing to disappear from recent textbooks. Accordingly, since it is granted that the problem is largely one of delivering sufficient iron to the bone marrow, the problem narrows itself down to arriving at the most efficient means of supplying the requisite amount of iron. In previous studies[1,2] we have used molybdenum ferrous sulfate orally and found that with the iron preparation and supplementation with intravenous iron, only 89 per cent of patients were brought through pregnancy with satisfactory hemoglobin levels. This is in contrast to figures given by Holly[3] which show that only 21.8 per cent of women will maintain their hemoglobin levels of early pregnancy if they do not receive supplementary iron throughout the pregnancy.

It has been well established that women absorb supplementary iron through the intestinal mucosa at a rate of only 5 mg. per day[4] and that they will have an iron deficit in pregnancy of about 700 mg. of iron, 500 mg. to the baby, 100 mg. in the placenta and 100 mg. in a normal blood loss. Hence, it is imperative that the pregnant woman receive at least 150 days of iron administration during the gestational period in order to anticipate this loss.

When in previous studies[1,2] there was a failure of the method in 10 per cent in prevention of anemia in pregnancy, attention was turned to the effect of adding cobalt to the iron ingested, as suggested by the work of several other investigators,[5-7] to improve the utilization of the iron dietary supplement. In this work the cobaltous chloride ferrous sulfate preparation used was Roncovite.† The amounts used originally were one tablet four times daily but there were many patients who improved on two tablets three times a day. The hemoglobin determinations in both Holly's series and my series were by photoelectric methods with the larger volume dilutions (Evelyn & Leitz technics) which we found to be parallel in previous studies.[1,2]

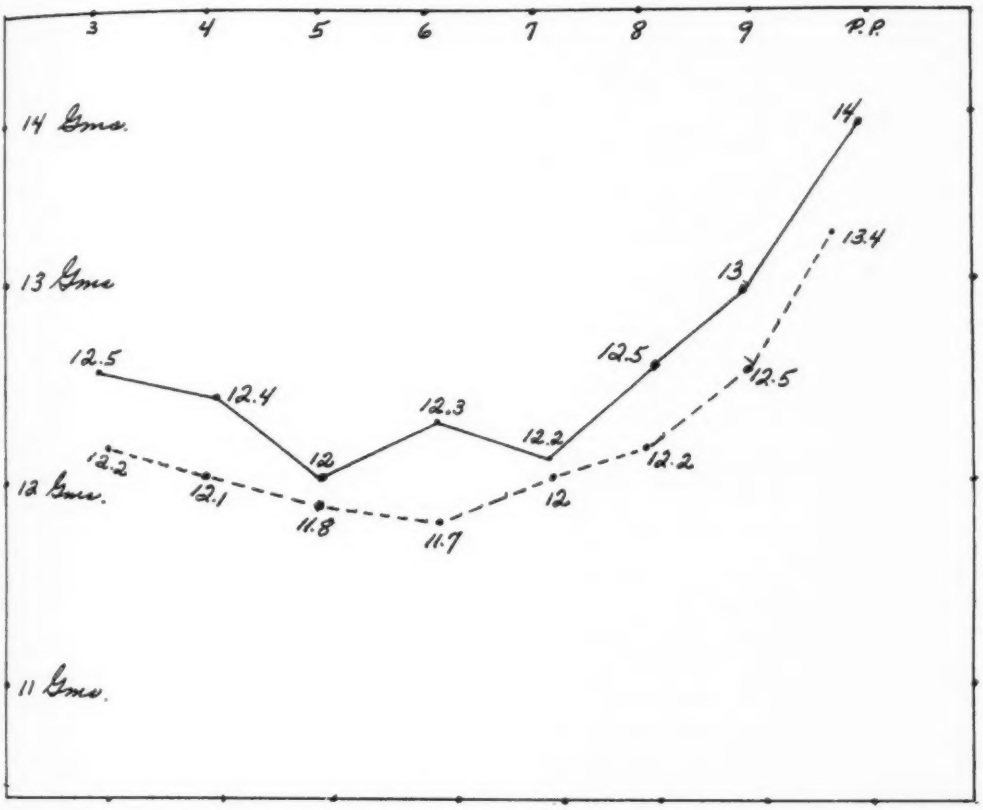
In comparing the monthly hemoglobin averages (Fig. 1) from the third to the ninth month of pregnancy and in puerperium, one observes that the curves run quite parallel until the last prenatal and the postnatal determinations, which are the true effects of the prolonged therapy. I feel the dip around the fifth month is due to the fact that in many of our cases we found the dosage of one tablet four times a day was insufficient, and it was between this time and the seventh month that many had the dosage increased to two tablets three times per day.

At this point I might mention that when a woman has been placed on iron therapy orally and is not responding well it is wise to examine her rectally. If the finger cot is not properly stained black, a few choice and pointed remarks about people who do not follow orders will usually result in an improved response to iron therapy. Certainly in

*Read before the Section on Obstetrics, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

†Supplied by Lloyd Brothers, Inc.

FIG. 1



Solid Line. Hgb. at each month of pregnancy in 175 patients given iron with cobalt. Broken Line. Hgb. at each month of pregnancy in 1,746 patients given iron with molybdenum and iron intravenously.

figure 1 the iron cobalt group fare better in their final iron balance than do the iron molybdenum and intravenous iron group.

In table 1 are shown the hemoglobin values at the initial visit of the control group, as well as the group treated identically by Holly and by the author. In analyzing our data, Holly and I felt that the moderately higher hemoglobin levels at the initial visit observed in the author's series as compared to Holly's treated and control groups reflect the fact that his patients were clinic patients who un-

TABLE 1

HEMOGLOBIN VALUES AT INITIAL VISIT

Grams Hgb. per 100 cc.	Untreated*		Holly Treated		Hamilton Treated		Total Treated	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
9-9.9	0	0	0	0	0	0	0	0
10-10.9	5	9.1	12	17.1	3	2.9	15	8.6
11-11.9	15	27.2	20	28.6	22	20.9	42	24
12-12.9	20	36.5	24	34.3	41	39	63	36
13+	15	27.2	14	20	39	37.2	53	31.4
Total	55	100	70	100	105	100	175	100

*Previously published by Roy G. Holly3

TABLE 2

HEMOGLOBIN VALUES AT PREDELIVERY VISIT

Grams Hgb. per 100 cc.	Untreated*		Holly Treated		Hamilton Treated		Total Treated	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
9-9.9	6	10.9	0	0	0	0	0	0
10-10.9	17	30.8	1	1.4	0	0	1	0.6
11-11.9	13	23.7	9	12.8	11	10.5	20	11.4
12-12.9	13	23.7	19	27.1	25	23.5	44	25.2
13+	6	10.9	41	59.7	69	66	110	62.8
Total	55	100	70	100	105	100	175	100

*Previously published by Roy G. Holly[3]

doubtedly did not follow as sound dietary practices as did the private patients in my series. Even so I shudder occasionally when I inquire of some of them about their dietary habits.

While the eventual postpartum hemoglobin levels are important as they reflect the final hematologic condition of the patient after pregnancy and parturition, from the standpoint of the obstetrician the final predelivery level is most significant as that reflects the condition of the woman whose labor he is about to conduct. In table 2 it is clearly spelled out that iron therapy is essential to maintenance of hemoglobin in pregnancy. It is interesting to note that under the influence of cobalt-iron therapy the initial hemoglobin advantage of the private patient's better nutritional status is largely wiped out by the time full-term has been reached. Incidentally, Holly deeply regrets that he did not apply the rectal examination test of iron therapy to the one patient in his treated series whose hemoglobin fell below 11 Gm. per 100 cc.

Table 3 shows clearly the effects of cobalt-iron therapy as compared to the control series in which patients received no supplementary iron; the regular deterioration in the untreated series is brought out.

TABLE 3

COMPARISON OF TREATED AND UNTREATED CASES

Grams Hgb. per 100 cc.	Per cent Untreated 55 Cases		Per cent Treated 175 Cases	
	Initial Visit	Predelivery Visit	Initial Visit	Predelivery Visit
9-9.9	0	10.9	0	0
10-10.9	9.1	30.8	8.6	0.6
11-11.9	27.2	23.7	24	11.4
12-12.9	36.5	23.7	36	25.2
13+	27.2	10.9	31.4	62.8

Table 4 should still any lingering memory of the "physiological" anemia of pregnancy, since there is true anemia in the treated group in less than 1 per cent of cases and true anemia in 41.7 per cent of the untreated cases. With the studies on the treated series being done in two different cities, in two different laboratories, by four different technicians and upon two different classes of patients, and with treatment results checking within 1 per cent, we feel that the two series of treated cases corroborate each other fully.

TABLE 4

Grams Hgb. per 100 cc.	55 Untreated Cases at Delivery		175 Treated Cases at Delivery	
	Number	Per cent	Number	Per cent
13+ Gms. Hgb.	6	10.9	110	62.8
12+ Gms. Hgb.	19	34.5	154	89
11+ Gms. Hgb.	32	58.3	174	99.4
Anemic	23	41.7	1	0.6

Table 5 shows the method failures. The three cases of gastrointestinal irritation are about what one would expect. There are certain individuals to whose gastrointestinal tracts ferrous sulfate is irritating, causing either pain or diarrhea, although their actual number is small. The orally administered liquid iron preparation used successfully in all three instances (Proferrin)* has been used by me before and usually is well tolerated by those whose gastrointestinal tract is sensitive to ferrous sulfate. It usually will maintain hemoglobin levels satisfactorily.

Of the three patients who failed to absorb iron properly and had to be treated by intra-

*Supplied by Sharp & Dohme.

TABLE 5

METHOD FAILURES

7 Patients.	Withdrawn from series in addition to 105 reported
3 Patients.	Gastrointestinal irritation successfully treated with iron monoxide in monosaccharide orally (Proferrin—S. & D.)
3 Patients.	Failure to absorb from the intestine, successfully treated with 900 mg. of Proferrin (S. & D.) intravenously. Two of these had to have iron intravenously for same reason in previous pregnancy when given ferrous sulfate with molybdenum (White).
1 Patient.	Refused to swallow "pills," therefore successfully treated with 900 mg. Proferrin (S. & D.) intravenously.

venously administered iron monoxide (900 mg. in broken doses) all three responded satisfactorily. It is interesting to note that two of these three patients had failed in prior pregnancies to absorb iron properly when given molybdenum ferrous sulfate and had been similarly successfully treated by the same dosage of the same preparation. The fourth patient who refused to swallow pills must be classed as a method failure.

There has been considerable furor of late about the toxic effects of cobalt. Much of this seems to stem from a very small group and involve very few cases with some series of cases refuting this. Quilligan[8] and Hill,[9] to mention a few, certainly have had no such toxic effects. In this 175 cases we have seen a few instances of mild skin rash which disappeared upon withdrawal of cobalt and did not always recur upon readministration of the drug. Because of the discussion of thyroid hyperplasia due to cobalt the patients have been observed for this and no more enlargement of the neck was found than is usually seen. Each of the newborn children of the mothers treated with cobalt and iron have been cared for by competent pediatricians and no untoward effects have been observed in these offspring.

Conclusions

1. There is no "physiological" anemia in pregnancy, only (except rarely) anemia of iron deficiency.

2. Iron therapy should be started at least 150 days prior to delivery.

3. Iron therapy utilizing ferrous sulfate cobaltous chloride has been our most satisfactory method to date.

4. The usual method failures will occur with this treatment but their number is small and they can be successfully combated.

5. No toxic or other untoward effects were observed in this series of cases using cobalt-iron therapy.

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Discussion (Abstract)

Dr. Garth L. Jarvis, Galveston, Tex. Dr. Hamilton again brings to us a report of his continuing work with the so-called physiologic anemias of pregnancy. It is true that there is actually an increase of the total number of red cells, the total cell volume and the total amount of hemoglobin in the body of the pregnant woman, but since this is much less than the total increase in the blood volume we have present the same conditions as we have with the decrease in these factors in a normal blood volume. Therefore, it is of great importance that we continue to consider the problem of anemia in pregnancy and a better method of therapy than plain ferrous sulphate with a high instance of intoleration in effectiveness.

I have agreed with most of Dr. Hamilton's previous reports, but in this particular case, The Use of Cobalt and Iron in the Prevention of Anemia of Pregnancy, it is necessary that I view it with much less enthusiasm. In fact, it is with alarm that I consider what might happen if it is used universally without a great deal more evaluation. One only has to read the multitude of papers which report the many complications with the use of cobalt and to hang up a red light, or at least a caution light, about its routine use. Certainly one must consider the reports of hyperplasia of the thyroid with later signs of hyperthyroidism, anorexia, nausea, vomiting, eighth nerve damage with tinnitus and deafness, claudication of the leg muscles, severe substernal pain, etc., before endorsing such a product for use. Potential dangers must be carefully weighed against the possible advantages of the therapy.

In Dr. Hamilton's series there have been no fetal nor maternal complications other than an occasional rash, but apparently we must only sit back and let him report them in the future. In the August issue of the journal, *Blood,* there is a report of a panel discussion on the use of cobalt in anemias. The almost

unanimous opinion of the hematologists is that the dangers of the use of cobalt far outweigh any advantages. I talked with Dr. Rundles, Professor of Hematology at Duke, and he stated that all cobalt did was to give the patient polycythemia, much the same as one gets in going up in a balloon, and to make them feel worse than they did prior to such treatment.

Actually, there is evidence that cobalt in some way interferes with the oxygen-carrying capacity of the hemoglobin, and the ensuing anoxia causes the development of polycythemia such as is seen in people living in very high altitudes.

I, personally, would discourage the use of cobalt and iron therapy in routine practice and, instead, use it only as a carefully controlled research project, pending further reports.

I want to thank Dr. Hamilton for the privilege of previewing and discussing this fine paper. I hope that Dr. Hamilton will continue his research on the treatment of the anemias of pregnancy.

Dr. Hamilton (Closing). These reports of toxicity have, in large part, originated from the treatment of premature and newborn infants. The work that originally started a lot of the discussion on thyroid hyperplasia, came from the San Francisco Bay area, involving some five cases which have been analyzed and reanalyzed now at four different times. Investigators in Toronto, if I remember correctly, after being unsuccessful in producing hyperplasia in animals tried to produce the hyperplasia in children, and failed utterly.

In addition to that, Dr. Klinck, in Washington, D. C., has also worked on the problem, and has come to the conclusion that a good proportion of the thyroid hyperplasia which has been discussed has been a factitious thing.

I understand a case of infant thyroid hyperplasia following the use of cobalt was reported at one of the other meetings today. I am sorry I could not attend for I would like to have heard what they had to say. Remember this, there is no heavy metal that is not toxic when it is given in sufficient quantities or to people who have more sensitivity than others. These patients are supposed to be observed as they go along, and under observation, one should recognize any reaction. After all, reasoning on an analogy, it is just as valid to say one should not give iron because we know of dead children who got into their mother's iron pills.

Psittacosis (Ornithosis) in Texas*

J. V. IRONS, Sc.D., *Austin, Tex.*, DON MASON, D.V.M., and R. F. WHITE, M.D.,† *Atlanta, Ga.*

Ornithosis is to be kept in mind in cases of viral pneumonia, especially if the patient's occupation involves the handling of fowl.

PSITTACOSIS (ORNITHOSIS) IN MAN has been attributed both to psittacine and nonpsittacine birds, including pigeons,[1] chickens,[2] ducks,[3] pheasants,[4] and turkeys.[5] Ornithosis-like viruses have been recovered from several species of animals, but the significance of these agents as human pathogens has not been determined.

Ornithosis or ornithosis-like viruses have been recovered from the willet,[6] parakeets, and turkeys[7-9] in Texas. Serologic evidence of infection has been found in several species of birds. Previous reports by our co-workers and by us[5,8] have concerned five outbreaks of ornithosis attributed to dressing turkeys in Texas. These outbreaks included at least 96 cases with 7 deaths and occurred from November, 1948, through December, 1952, in two establishments. Since 1952, when psittacosis became reportable in Texas, 264 cases have been reported to the State Department of Health. These cases were practically all attributed to dressing turkeys; 201 of the 264 cases were reported in 1954.

The present report concerns cases of turkey ornithosis in man in 1954 confirmed by the laboratory, some observations regarding the outbreaks or cases, and a few miscellaneous cases of psittacosis or ornithosis in Texas in recent years.

Clinical and Laboratory Findings in Outbreaks in Turkey Processing Plants

The severity of the illness varied from mild influenza-like attacks to severe illness requiring hospitalization. The onset generally was characterized by chilly sensations, fever, malaise, headache and sometimes nausea and vomiting. After a few days the patients frequently felt much worse. The duration of the illness varied from a few days to a few weeks. Many of the patients were ill two or three weeks. Although relatively few complained of cough, some complained of soreness in the chest.

Physical signs referable to the chest were not very obvious. Fine rales frequently were heard but areas of consolidation were not detected. On the other hand, x-ray films usually demonstrated a patchy pneumonitis, most prominent in the area of the hilar and main stem bronchi. Several patients in most outbreaks had one or more relapses. Convalescence sometimes was prolonged for several weeks or a few months. The broad spectrum antibiotics were used with apparent success. The only death occurred in a patient treated with penicillin, after a great deal of delay.

Perhaps it was not surprising that cases in women predominated because of the occupational groups exposed to infection. The illness was milder in the younger workers, who also appeared to be less susceptible. Diagnosis was established on the basis of occupational, epidemiologic, clinical, and laboratory findings.

Laboratory findings were most noteworthy. The leukocyte counts frequently were in the normal range. Febrile agglutination tests were negative on the several cases tested. The complement fixation test utilizing LGV or psittacosis antigen was the most useful of the laboratory aids. The recovery of the agent from the patient's throat washing, sputum, or blood was successful only on one occasion, perhaps because of the early use of broad spectrum antibiotic therapy. The complement fixing titers varied greatly. There was considerable evidence that intensive broad spectrum antibiotic therapy delayed or suppressed the titer particularly when early treatment dramatically aborted the infection. Patients having relapses also frequently showed poor

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serologic response. At least one blood specimen was obtained in a high percentage of cases, and paired or serial bloods were obtained in many cases. Laboratory confirmation was based on the demonstration of a rising titer in convalescence or shortly after recovery, an apparent elevation of the titer, or a decline in titer after recovery from illness, as shown in table 1. Significant fourfold or greater increases in titer were demonstrated in a considerable number of cases in eight cities.

Epidemiologic Findings

The marketing and dressing of turkeys is primarily seasonal and limited to periods before Thanksgiving and Christmas, and at the end of the egg-laying season. The 1954 outbreaks occurred near the end of the egg-laying season. Apparently there was nothing unusual about the construction or the manner of operation of the involved plants. In all the plants there are a number of machine operations in the removal of feathers and other procedures which produce air-borne particles. The highest attack rates were in those employed as eviscerators or pickers and exposed to air-borne infection, in addition to the hazards of direct contact. Lower attack rates prevailed in employees of the trucking and receiving departments. Attack rates were quite low among workers in the cooling room and the packing departments, suggesting that if infection was the result of direct contact the hazard had been minimized in the fully dressed turkeys.

TABLE 1

TABULATION OF LABORATORY-CONFIRMED 1954 CASES OF TURKEY ORNITHOSIS IN MAN IN TEXAS

City	*No. of cases reported*	*No. of cases laboratory confirmed*	*No. of laboratory-confirmed cases showing fourfold or greater increase in titer*
Corsicana	48	43	33
Brady	69	43	19
Lampasas	40	29	15
Austin	0	5	2
San Antonio	1	1	1
La Grange or Fort Worth	0	1	1
Taylor	24	16	10
Comanche	6	5	2
Armed Forces*	2	0	
Total	190	143	83

*Infections acquired at Brady Plant

The first outbreak of ornithosis in 1954 occurred at Corsicana, where a local poultry plant had processed a single flock of 469 turkeys on April 1. The ornithosis virus was recovered from some of these turkeys shortly after they were rushed to market without our knowledge. The first illness was noted on April 7. During the next week or ten days 47 additional cases occurred in a group of 79 persons employed in the plant. Thirty-four patients were hospitalized. All of those ill with one exception had helped dress the lot of turkeys on April 1. The one exception was a young woman who did not work at the plant on April 1, but who had laundered the clothing of her father and two brothers who were ill.

Most of the outbreaks were explosive in nature and suggested that single flocks were responsible; but, notably, in two of the plants where infected turkeys were processed at intervals, infections appeared in waves over a period of a few weeks. At least 71 cases were recognized in a plant at Brady, as shown in table 1. The number of the workers who became ill in plants where infected turkeys were processed varied from 0 to nearly 90 per cent. Although both turkeys and chickens were processed in most of the involved plants, there was no evidence that chickens were a source of infection.

During or shortly after the course of the outbreaks several flocks were singled out as sources of infection. In a few flocks the infection was suspected before the turkeys were rushed to market. In two plants the outbreaks were predicted almost to the day of the first case, although laboratory confirmation was not obtained before the turkeys were taken to market. The virus was recovered from turkeys on at least 12 farms in three distinct areas of the state. Other flocks obviously were sources of infection on the basis of epidemiologic or serologic findings. In all plants where outbreaks occurred there was good evidence that sizable infected flocks of turkeys were sources of infection. In retrospect the outbreaks in the processing plants also indicated a relationship with acute or subacute epizootics in certain flocks of turkeys.

Epizootiology and Control Measures

The recognition of an epizootic by the buyers for processing plants presented the greatest

difficulties. In fact, an epizootic could be identified only by recovery and identification of the virus in one or more turkeys. These epizootics were not dramatized by an explosive onset. Many of the birds had latent infections without obvious symptoms. Nevertheless, some of the birds appeared ill. Such nonspecific symptoms as droopiness, weakness, anorexia, fever, yellowish green, soft to fluid feces, and occasional respiratory difficulty were seen. In two flocks of about 1,400 birds, about 100 deaths occurred over a three or four week period. Recovery from the infection was frequent. Egg production and hatching of eggs declined rapidly during the epizootic. Hens and toms appeared to be affected equally. Virus was recovered from birds showing little or no gross pathologic findings. The most prominent and consistent lesions were those of the serous membranes. A whitish plastic-like fibrinous film frequently was seen adherent to the liver. Pericarditis was a common finding. These findings are not pathognomonic and should be confirmed by a laboratory identification test.

Turkey farmers should be encouraged to seek a laboratory diagnosis of unidentified illnesses in their flocks, and actively infected flocks should be withheld from market. Poultry pathologists or veterinarians who are familiar with turkey ornithosis should be employed on the assembly lines in the processing plants to conduct postmortem investigations. Suspicious lesions should be submitted to a competent laboratory for tests. The disease should be recognized as an occupational disease for which the infected workers should receive a fair compensation, and recently has been so defined under the workmen's compensation law of Texas.

In view of failure to find the virus in dead turkey embryos or young poults, it was theorized that the turkey flocks had become infected from feeding with other birds. There was no good evidence that parakeets were the source of infection. A suspicious serologic reaction was obtained on a wild turkey from another area of the state, but the virus was not recovered from wild turkeys. Wild turkeys frequently feed with domestic turkeys. Several English sparrows, doves and pigeons similarly did not yield the turkey ornithosis virus. It has been suggested that the Texas turkey ornithosis virus may be more closely related to the Louisiana human and the egret strains[9] than to the parakeet virus, but further studies are needed. In view of the public health and economic problems, it is evident that much more research is needed.

TABLE 2

LABORATORY-CONFIRMED CASES OF ORNITHOSIS OTHER THAN THOSE ACQUIRED FROM TURKEYS, BY SOURCE AND YEAR

Source	*1952*	*1953*	*1954*	*1955*
Parakeet	2	4	8	6
Parakeet or chicken			2	
"Road runner"			1	
Unknown	1	2		

Human Infections from Other Sources

Most of the proved cases of ornithosis other than those attributed to turkeys have been attributed to parakeets. The virus was identified in one or more parakeets from five aviaries in the investigation of infections from parakeets. Two cases in farmers possibly were acquired from contact with chickens. One case was attributed to contact with a "road runner" which was killed by an automobile. The distribution of cases confirmed by laboratory tests in recent years is shown in table 2.

Summary

Some of the features of ornithosis in Texas in recent years have been described. The most outstanding has been the emergence of turkey ornithosis as an occupational disease in several turkey processing plants. Turkey ornithosis outbreaks particularly were troublesome at the end of the egg-laying season in 1954.

Turkeys have considerably overshadowed parakeets as sources of recognized human infections in Texas in recent years. Some of the problems associated with turkey ornithosis and some suggestions regarding their partial solution were made. The need for more research on turkey ornithosis is evident.

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Discussion (Abstract)

Dr. Fred K. Laurentz, Houston, Tex. The essayists are to be congratulated for this report on some of the features of turkey ornithosis as it has appeared in workers in turkey processing plants. It seems obvious that the disease has become an occupational disease in certain plants, and is likely to appear again in the future. We have not been aware of any cases of ornithosis in employees of the poultry dressing establishments in Houston. However, I understand that blood tests which have been done in the State Health Laboratory under Dr. Irons' direction have suggested that such infections may have occurred in recent years. I would like to re-emphasize that physicians who see obscure cases of viral pneumonia should consider the possibility of ornithosis. It would be well to question these patients regarding any occupational history which would suggest this infection. When a suggestive history is obtained it would be well to apply the laboratory tests necessary in the recognition of this disease.

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PANEL DISCUSSION

Medical Versus Surgical Treatment of Gastric Ulcer*

MODERATOR: MICHAEL E. DeBAKEY, M.D., *Houston, Tex.*
PANELISTS: R. L. SANDERS, M.D., *Memphis, Tenn.*, CARL E. LISCHER, M.D., *St. Louis, Mo.*, JULIAN M. RUFFIN, M.D., *Durham, N. C.*, and JOSEPH B. KIRSNER, M.D., *Chicago, Ill.*

A discussion of the medical and surgical aspects of the management of gastric ulcer always provides controversy and sharp disagreement.

Dr. Kirsner: Since the fundamental etiology of peptic ulcer is not known, there are certain gaps in our knowledge of its pathogenesis. As I understand the problem, clinically and experimentally, at least two factors are concerned in the development of peptic ulcer,—acid-pepsin digestion and tissue vulnerability. In duodenal ulcer the output of hydrochloric acid is excessive and is presumed to be enough to overcome the normal resistance of the duodenal mucosa. In gastric ulcer the output of acid is normal or less than normal; in this situation tissue vulnerability assumes an important, perhaps determining factor. However, even under these circumstances, complete elimination of the acid of the stomach will lead to complete and sustained healing regardless of other theoretical or actual considerations. From this physiologic point of view, then, gastric ulcer and duodenal ulcer are the same pathogenetically. They respond in the same way to adequate control of acid secretion. Failures in the medical management of gastric ulcer are attributable to inadequate control of the acid gastric secretion, and reflect inadequate methods of treatment, not necessarily a flaw in the theory.

Now, from the standpoint of other aspects of the problem, we also know that gastric ulcer proportionately occurs more frequently in women than does duodenal ulcer. There are interesting differences in the personality patterns of patients with gastric ulcer and those with duodenal ulcer, based, I may add, upon subjective analyses rather than objective data. There are certain differences in the course of the disease also, but the two problems especially characterizing gastric ulcer from duodenal ulcer are: the differential diagnosis of benign and malignant ulcer, and the possibility of malignant transformation of a benign gastric ulcer. There has been much written on the subject of "ulcer-cancer," most of it philosophic rather than scientific. The incidence of "carcinoma from ulcer" in the world's literature varies from zero to 100 per cent. In my experience, the benign gastric ulcer remains benign and does not undergo neoplasia. The carcinomas that are diagnosed subsequently represent failures in proper diagnosis. Various attempts have been made to characterize the theoretical transformation of the benign gastric ulcer on clinical information and upon certain criteria. These indices are not entirely satisfactory and, in our experience, not entirely acceptable. Because of the limitations of time, I prefer not to discuss this phase of the problem in detail. The incidence of carcinoma of the stomach in patients with gastric ulcer is no higher than one would expect in the same age population without gastric ulcer. I do not consider gastric ulcer a precancerous lesion. The prolonged observation of many patients with gastric ulcer for many years has not disclosed an increased incidence of gastric malignancy.

*Presented before the Section on Gastroenterology, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

A major question in this entire discussion, of course, is the differential diagnosis between benign and malignant gastric ulcer. The problem is difficult and it has been confused further by inaccurate statistics and data based upon inadequate or unacceptable criteria. Just as it is not proper to compare a minor league team with a major league team, so it is not appropriate to compare the approach of a general practitioner to the problem of diagnosis of gastric ulcer with that of the experienced gastroenterologic internist. In our own experience, an accurate differential diagnosis is possible in 95 per cent of cases, provided all diagnostic methods are used, skillfully and repeatedly and all the information is carefully integrated and analyzed. Our error in diagnosis is 5 per cent, no higher than the mortality rate of gastric surgery in the hands of many surgeons; of course, we are as unhappy with our diagnostic errors as the surgeon is with his operative failures. The various diagnostic methods include a careful clinical history and physical examination; though not decisive in every case, they can be most helpful. The x-ray, of course, is very important. Gastroscopic examination, which we employ in all cases of gastric ulcer, can be very important when used properly. The potential dangers of gastroscopy have been mentioned. There are hazards, of course, with any diagnostic and therapeutic procedure. Some people may conclude, as I do, that the risk of careful, skilled observation is no greater than the risk of surgery.

Exfoliative cytologic study of the stomach is in the developmental stage but very useful in our experience. We utilize this procedure almost routinely and we find it to be of great help. New methods are constantly being developed, promising to increase further the accuracy of the method, including fluorescent scanning technics. Other possible diagnostic approaches include the electrogastrogram and rapid fluoroscopy of the gastrointestinal tract; I am not sufficiently familiar with these methods, but I think they are not of decisive importance at the present time.

Dr. Ruffin: I have been asked to comment briefly on the medical management of gastric ulcer. As far as I am concerned the medical management of gastric ulcer is identical with that of duodenal ulcer. The usual ulcer diet, antacids, anticholinergic drugs and sedatives are all employed. If one has a deep, penetrating ulcer the problem becomes more difficult and obviously more intensive therapy is required. Overnight gastric suction with feedings during the day, or even constant suction for several days is definitely indicated in such cases. The danger of perforating the ulcer by such a procedure is minimal and should be ignored. Anticholinergic drugs given parenterally have proved extremely valuable in our experience. All of these patients should be hospitalized and their course followed closely by x-ray or by gastroscopy to observe proper healing, preferably at weekly intervals. After healing has taken place, they should have the usual interim care of the ulcer patient.

While the location of a duodenal ulcer has little effect upon the treatment which is recommended, the location of a gastric ulcer, on the contrary, profoundly affects our thinking. If one has a gastric ulcer high up in the cardia, I think the surgeons will agree that removal is technically difficult, requiring total gastrectomy, and therefore, these patients should be handled medically if possible.

An ulcer on the greater curvature, on the other hand, is another matter. Although all of us know that there have been proven cases of benign ulcer on the greater curvature, I think it the part of wisdom to go ahead and resect them without delay because of the danger of malignancy.

If one has an ulcer in the pyloric channel this presents a more difficult problem in treatment. We have recently collected 100 consecutive cases of channel ulcer, and interestingly enough, not a single one of these has proved to be malignant. With intensive therapy, anticholinergic drugs, gastric suction, and so forth, they do very nicely, rarely requiring surgery. Now, what is the result of medical management of gastric ulcer? Our results are fine. The usual ulcer will heal under medical management. The ones that do not heal, are not only the carcinomatous group which have been misdiagnosed, but the deep penetrating ulcer that is plastered down against the pancreas. As pointed out in our paper read by Dr. Sohmer, *(South. M. J.* 49:393, 1956) there may be two components of ulcer pain, namely visceral and somatic. The patient whose pain radiates to the back, around the chest wall, to the shoulder or over the precordium has involvement of the somatic nerves. This usually means that there is an

inflammatory mass in the vicinity of the ulcer. These patients respond poorly to medical management. If, after a short period of hospitalization, they have not recovered, they should be resected promptly.

Dr. Lischer: Well, I should think we might as well get the controversy under way, and as a surgeon, I will state my position and try to present this very briefly. I think that gastric ulcer is primarily a surgical problem and I shall try to give some reasons to support that idea.

In the first place, I am sure, as Dr. Sanders will emphasize, it is difficult in many cases to be sure whether the ulcer is malignant or benign. I agree with Dr. Kirsner that rarely does a benign ulcer become malignant. However, in a good many large series of reported cases, the incidence of malignant ulcer, found in cases diagnosed as benign ulcer preoperatively, has been high enough to justify the position that it is difficult to be sure whether a gastric ulcer is benign or malignant. At the Lahey Clinic it was found in 600 some-odd cases of clinically benign gastric ulcers that 21 per cent were found to be malignant after their removal. Such a figure is a little too high to be complacent about regarding the possibility of benignancy or malignancy.

There were 73 patients at the Mayo Clinic who were diagnosed as having benign gastric ulcers that were found to have cancer of the stomach on pathologic examination of the resected specimens. Forty-three per cent of these were alive at the end of five years. So you can see that in this group of patients with gastric ulcers which were malignant, although diagnosed as benign preoperatively, the prognosis is good and is relatively the same as the prognosis of cancer of the stomach when it is confined to the stomach, which gives a cure rate of 45 to 50 per cent.

The mortality rate following gastrectomy for a gastric ulcer is far less than it is for duodenal ulcer, and I think we ought to distinguish between the two. Most of the mortality from gastrectomy follows trouble with the duodenal stump, or from thromboembolic phenomena. Now, in gastrectomy for gastric ulcer there is a very low mortality and it is in the same neighborhood as that of the operative mortality for cholecystectomy.

As to the morbidity following gastrectomy for gastric ulcer: True, there is some morbidity, but if the patient has a gastric ulcer and not a duodenal ulcer, the appearance of a stomal ulcer following gastrectomy is almost unknown. Such patients hardly ever develop marginal ulcers and the appearance of cancer in the gastric remnant is also rare. There are reports where symptoms persisted for a long period of time under medical management. If these patients are followed for 10 years, rather than for a shorter period of time, the number who have a recurrence of symptoms increases as the period of time lengthens during their medical management.

I would like to say that my position is this. First there are many gastric ulcers which the surgeon never sees, the small ones which heal promptly. In the majority of cases, according to some gastroenterologists, gastric ulcers fail to respond to conservative therapy. In approaching the problem surgically, I think the patient with a gastric ulcer, whether it is diagnosed as benign or malignant, should have a subtotal radical resection, as an initial procedure, with a few exceptions which I will mention in a minute. By subtotal radical resection, I mean removal of the gastrohepatic omentum, the gastrocolic omentum, the greater omentum, part of the duodenum, all of the nodes in the pyloric area and around the left gastric artery, the celiac axis and the splenic group of nodes. One can leave a gastric remnant which does not cripple a patient nearly so much as a total gastrectomy.

The two exceptions to this procedure would be, one, an ulcer at the esophagogastric junction which may be very difficult to handle in this manner, and the other is the huge penetrating ulcer which, in my experience of nine such cases, have all been benign. In a huge ulcer,—and by huge I mean more than 7 or 8 cm. in diameter,—the wall of the stomach is destroyed and the adjacent organ forms the base of the ulcer, commonly this is the pancreas. If this is recognized as benign, a very complex situation is converted into a simple one, and a gastrectomy is done without sacrificing the adjacent organs. These patients are usually old and usually in poor nutritional status.

This slide shows an ulcer with radiologic evidence of being benign, and also shows some evidence of healing.

In this one likewise, at first examination, was thought to be benign, had radiating

mucosal folds into the ulcer crater and showed evidence of healing in the follow-up treatment. Both of these patients later had recurrence of symptoms, were operated on and both had carcinoma of the stomach.

Now here you see a huge ulcer of the kind I am talking about. This ulcer was at least 9 centimeters in diameter. This man had had a cerebrovascular accident, had lost 40 pounds, and was in very poor condition. The radiologist tried to call this a lymphosarcoma.

At exploration this huge ulcer crater was removed from its base. This ulcer was benign as proven by multiple frozen sections. A very complex situation of resecting the stomach and pancreas in a man who was an extremely poor risk, was converted into a simple problem.

Thank you.

Dr. Sanders: Mr. Moderator, I came up in the days when this problem was in its infancy. It has been nearly 40 years since I started thinking of the problem of gastric and duodenal ulcers. Dr. W. J. Mayo, under whom I trained, remarked that after "nine complete and permanent medical cures," he considered them surgical. It has been very difficult for me to get away from that thought, particularly when the ulcer is on the gastric side of the pylorus. I agree with anyone who treats a duodenal ulcer medically over a long period of time, until complications arise which require surgery. When a penetrating gastric ulcer is present, however, I am not so sure I can go along with that type of treatment.

Of course, we know the pylorus is the deadline across which cancer dare not pass, and of the many cases I have seen during the past 40 years, I have yet to find a malignancy in the duodenum. I can say to my medical confreres, I am not afraid of cancer in a duodenal ulcer, and I can tell the patients the same. But when an ulcer is encountered on the gastric side, no matter where its location may be, we become suspicious, and more and more we are convinced that the best treatment is to remove the ulcer, and if an early carcinoma exists there is still a chance to control it.

I am not an advocate of the theory that all gastric ulcers degenerate into malignancy, although I am immediately suspicious when it cannot be determined clinically, from roentgenograms, from symptoms, or by any of our diagnostic methods, whether a benign condition exists. With the abdomen open and the stomach in one's hand, the appearance and feel of it will give one a fairly good idea as to whether it is a malignant or benign ulcer. I am frank to confess after having seen many, and after investigating more than 500 of these cases, I am still in doubt, and when in doubt, I lean toward the surgical side.

As Dr. Lischer has done, I too would like to show a few slides and give my reaction to the treatment of ulcers. I must admit I am on the conservative side in the treatment of duodenal ulcer. Eighty per cent or more of them are handled medically and are handled well, as are many of the gastric ulcers. But our concern is, which ulcer can be safely treated medically and which should have surgical treatment.

This slide shows a gastric ulcer. As you see, it is on the lesser curvature; the radiologist thought it was a gastric ulcer, and we thought so too. The patient's history and findings indicated it was. We resected the stomach because she was having a tremendous amount of pain which radiated to the back, indicating the pancreas was involved. When the abdomen was opened, from the appearance of the inflammatory reaction, we were sure it was a gastric ulcer, but when the pathologist had finished, it was adenocarcinoma. A good many years have passed since that patient was operated upon, and she is still well. Had resection not been done at that time, I am afraid we would have had an early death because of the ulceration which turned out to be malignant.

(Slide) Here is a definite penetrating ulcer. This patient was treated medically for a while, but the ulcer remained, and we could not cause it to disappear. Resection was carried out, and it was a benign gastric ulcer.

(Slide) Here is another which appears to be somewhat on the lesser curvature. Incidentally, I have seen very few benign ulcers on the greater curvature. In the territory in and around Memphis, Tennessee, where I am from, the patients just do not grow them on the greater curvature; most of them are on the lesser curvature, and a good many of them near the pylorus.

(Slide) This again, we diagnosed as a penetrating gastric ulcer, and we felt it wise to proceed with the operation. When the resection was done, early carcinomatous cells were

found at the base of this ulcer. Naturally, we were pleased to have got that one early.

I feel that many of these ulcers start as definite malignant ulcers and are not benign ulcers which become malignant.

(Slide) Here is a case which we thought was definitely a malignancy at the pyloric channel, as Dr. Ruffin mentioned a few minutes ago. Our medical service treated this patient for a while but the condition persisted. We resected her and the ulcer turned out to be a carcinoma on the gastric side.

We cannot diagnose benign ulcers in a high percentage of our cases.

(Slide) Here is another whose symptoms led us to believe this was a definite ulcer, but at operation we discovered carcinoma. You will note every other slide shown is cancer, but I am just showing you the difference in cases and emphasizing the point that we find it difficult to determine which are benign and which are malignant.

(Slide) This is a most interesting case of a young man who had a malignant melanoma on the sole of his foot. It was excised, and one year later he came in as an emergency with terrific pain. He was received in the emergency room and operation was done at once. The abdomen was opened, and we saw a definite small perforation on the lesser curvature which appeared to be a benign perforated gastric ulcer. Being of the opinion we should resect many of the perforated ulcers,—and we are resecting most of them now,—we decided to proceed with resection. To our great surprise, this was a tremendous melanotic carcinomatous ulcer with the small perforation that you see here (indicating). This proved to be a malignant perforating ulcer and not a benign ulcer. Of course, that was unusual,—it is the only one I have ever seen,—a melanotic perforating ulcer of the stomach.

(Slide) This is a definite penetrating ulcer of the stomach. This lady came to us a year and a half ago with severe symptoms of pain and discomfort. We decided she had a large ulcer on the lesser curvature and should have an operation because of the possibility of a malignancy. She said, "No" to operation, and my associates went on to treat it medically. She returned in three months and there was the ulcer, but it was very much smaller. A few days ago, after a year and a half, she returned again, and you see it is gone entirely. Here, then, is a large, penetrating ulcer which we have seen subside under medical treatment. We are now rather proud the lady said "No" to the operation, because we believe this is a benign ulcer which has properly healed under treatment.

I continue to belong to the group that shivers and shakes when a penetrating gastric ulcer is seen. About 20 per cent of the large number we have had turned out to be malignant when we thought they were benign, or benign when we thought they were malignant. The high percentage of malignancies at the bases of the gastric ulcers led us to surgical intervention in a high percentage of cases.

Moderator DeBakey: *I would like to return now to one of the first aspects of the problem, and that is the one concerned with the concept of gastric ulcers and duodenal ulcers. There are certainly differences in their management, their behavior after treatment. Do you want to start off, Dr. Kirsner?*

Dr. Kirsner: Well, my position continues to be the same, namely that acid-pepsin digestion and tissue vulnerability are the two physiologic disturbances we can identify at the present time. I am not irrevocably devoted to the term peptic ulcer. Gastric ulcer and duodenal ulcer would be perfectly acceptable terms, just so long as we understood that acid-pepsin digestion and tissue vulnerability were important factors in the development of the lesion.

Moderator DeBakey: *You agree, however, to merely use the term peptic ulcer does not define the problem?*

Dr. Kirsner: I think you are substituting one term for another without necessarily clarifying the issue. Gastric ulcer and duodenal ulcer localize the lesion; they convey nothing about pathogenesis. The advocates of peptic ulcer will be inclined to say, "Well, you at least have the indication that pepsin indigestion is involved." As I say, it is not too important, just as long as one has an understanding of the underlying pathologic physiology.

Moderator DeBakey: *Doesn't it have significance, however, in creating less confusion in terms of the diagnostic and therapeutic management of the problem.*

Dr. Kirsner: Yes, I think it might. I think

at least the discussion can be evaluated and channeled along more definitive lines. For example, we do not have to worry about carcinoma in duodenal ulcer. I might add that there have been two pathologic studies indicating that gastric carcinoma may spread across the duodenum and not be restricted by the pylorus.

Moderator DeBakey: *Dr. Ruffin, do you want to comment on that?*

Dr. Ruffin: Well, I have no objection to dropping the term of peptic ulcer. It certainly means a great deal to know what one is dealing with, a gastric ulcer rather than a duodenal ulcer. They are two different problems, although I am unwilling to admit that they are two different ulcers. I think they are the same disease. Pathologically, they are certainly the same. I think all the members of the Panel have agreed that while the carcinoma may ulcerate, the benign ulcer does not become cancerous. So, the problem then is that in gastric ulcer, first, you have to decide, is it possible that this patient has cancer; and, secondly, is the treatment to be different, provided the ulcer does not heal?

Moderator DeBakey: *Dr. Ruffin, you say they are the same disease. How do you reconcile the fact that the behavior pattern of duodenal ulcer is certainly different from gastric ulcer in a number of ways?*

Dr. Ruffin: In what way?

Moderator DeBakey: Well, for one, the behavior pattern of duodenal ulcer responds to medical treatment.

Dr. Ruffin: Oh, no! It depends on who treats it.

Moderator DeBakey: *Well, in your own case, let me ask you about your own treatment, then.*

Dr. Ruffin: My results are excellent.

Moderator DeBakey: Both of them?

Dr. Ruffin: Yes. My observation is, unless you have a penetrating ulcer that goes through to the pancreas, the benign gastric ulcer responds to treatment just as well as the duodenal.

Moderator DeBakey: *Let me ask you a question, in the case of a duodenal ulcer is the responsibility as great as in the case of the gastric ulcer?*

Dr. Ruffin: Joe, you take that.

Dr. Kirsner: I will be happy to, Julian. I think there is a very clear answer to that question based upon the differences in gastric secretion. Stomal ulcers do not develop after resection for gastric ulcer because there is not much acid. They occur not infrequently after gastric resection for duodenal ulcer because the amount of hydrochloric acid is excessive and its digestive capacity exceeds the resistance of the jejunal mucosa.

As I indicated at the outset, the gastric ulcer patient has a low or normal secretory rate; the duodenal ulcer patient a high acid secretion. In gastric ulcer the mucosa is especially vulnerable, and large amounts of acid are not necessary in the development of the lesion.

The key to the whole question is this: If one had the magic key to turn off acid secretion the problem of benign ulcers would vanish, regardless of any other consideration. Hydrochloric acid is like the catalyst in a chemical reaction, remove the catalyst, and despite the presence of other ingredients the reaction will not ensue; the ulcer will not persist.

Moderator DeBakey: The trouble is, that the magic key to one is not the magic key to the other.

Dr. Kirsner: Oh, yes it is.

Moderator DeBakey: Well, it isn't in terms of practical therapy.

Dr. Kirsner: Now we are getting to another problem that I think is of considerable importance. I do not agree with those who cannot make the differential diagnosis. I have the greatest respect for Dr. Sanders and Dr. Lischer, but I do not think they have had the advantage of good diagnostic assistants.

Moderator DeBakey: *Dr. Lischer, do you want to comment upon the point we have just been discussing, regarding the differences?*

Dr. Lischer: Well, if we grant that the pathogenesis of acid-pepsin digestion is the same in the two types of ulcer, duodenal or gastric, there may still be a difference in the etiology. Dr. Kirsner is from Chicago and I hate to explore the etiology of these two lesions, but we might ask him what he thinks about the difference in etiology, one being hypersecretion of nervous origin, and the other, primarily, antral dysfunction. If we have different etiologic factors, I think the term peptic ulcer ought to be dropped.

Dr. Ruffin: Do you have proof of different etiologic factors?

Dr. Lischer: No, sir.

Moderator DeBakey: The difficulty is we do not have enough knowledge about etiology.

Dr. Kirsner: Of course, therein lies the problem of peptic ulcer. What is it that characterizes the ulcer patient and nonulcer person?

We are beginning to get evidence now that in patients with duodenal ulcer the number of parietal cells is increased. There probably are other mechanisms, humoral, neurogenic and chemical. Dr. Lischer has mentioned the antral mechanism; I don't wish to get involved in that problem. I would merely point out that Dr. Dragstedt, who has championed that view, concludes that regardless of the various secretory mechanisms involved, the acid-pepsin attack remains as an ultimate expression of a number of factors, known and unknown.

Moderator DeBakey: *Now, let's pass on. Oh, Dr. Sanders, do you want to comment on this?*

Dr. Sanders: My comment would be similar to my previous discussion. I definitely believe gastric and duodenal ulcers are different diseases. For years I used the term peptic ulcer, but as time has passed we have noted a definite clinical difference in the patients with these diseases. Dr. Ruffin mentioned that possibly more women have gastric ulcers than men. Of course, the reverse is true with the duodenal ulcer, and there may be a sex relation which we do not know about. A very high percentage of our patients who have duodenal ulcers are men, men of certain ages, men of certain occupations, but that has not been the situation with the gastric ulcer. As yet, we have not definitely decided whether the facts causing the ulcers are identical.

Why do men predominate with duodenal ulcers and women with gastric ulcers?

I still maintain my original opinion that we should regard the gastric ulcer as one with dangerous possibilities, and the duodenal ulcer as a benign condition; that is, they are two different types of disease and should be regarded as gastric ulcers and duodenal ulcers.

Moderator DeBakey: *Unless there are any other comments, the Panel will go on to the matter of diagnosis.*

Dr. Kirsner: I would like to tell you of a disturbing situation in our own hospital when surgeons undertake the clinical diagnosis of gastric lesions. One of my colleagues recently reviewed 135 patients with gastric neoplasms and discovered such preoperative diagnoses, later proven to be gastric carcinoma, as chronic cholecystitis, chronic appendicitis, chronic pancreatitis; that represents a lot of nonsense. They were not studying their patients; they were taking not even an educated guess. I think that, unfortunately, this experience is representative of many medical centers. Dr. Lischer mentioned a series of patients studied at the Lahey Clinic. I have a great respect for my friends at the Lahey Clinic, but I would like to point out that in their series of 1,000 patients, only 50 had had gastroscopy; 950 were not so examined. There was no mention made of cytologic studies. Now, if we are going to compare diagnostic ability and potential we ought to compare them on an equal basis. I think if you are willing to admit that you just do not have adequate facilities for proper diagnosis, then I think you are right in proceeding with surgery; it probably is the safest approach under those circumstances. However, I think the scientific aspect of this question: can one make an accurate differential diagnosis, is more important. I think accurate differentiation of benign and malignant ulceration is possible in the great majority of cases, though I would add that further improvements in diagnostic accuracy would be very welcome.

Dr. Lischer: I would like to say first that the two cases I showed in the first two slides with evidence of healing of gastric ulcer which later proved to be malignant, with subsequent gastrectomy, were studied radiologically, by exfoliative cytology and gastroscopy. The resident who did those gastrectomies said that if he had a gastric ulcer which did not heal after taking one package of "Tums," he would have a gastrectomy.

Certainly it is not my opinion that a surgeon should proceed on his own in gastric surgery without the help of the gastroenterologist. The cases that come to my care for gastrectomy are worked up in that manner. I think that exfoliating cytology and gastroscopy still leave a lot to be desired and are not as accurate as the radiologic examination, but helpful adjuncts.

Dr. Sanders: Dr. Kirsner sort of took me to task by implying I had some pretty poor

help in my diagnostic force, or else I was one of those little old country surgeons who did not make his own diagnosis. Well, I admit I am that type, but at the same time I am sorry I did not bring my internists with me and let them determine the situation for me. We have three internists and three surgeons in our group; the internists try their utmost to keep us from operating upon any of their patients until they make the diagnosis complete and use a medical trial. I must defend my medical associates; they are good diagnosticians and work out cases thoroughly before they are submitted to the surgeons. I am the last one to get the grab on them because they hold them just as long as they can before they come to me.

We tried gastroscopy for a while, and nobody could make the thing bend around the curve just right; neither did we have enough men who were specialists in that type of work. It may be valuable, but it has not proved to be of value to us.

Dr. Ruffin: My experience has been about that of Dr. Kirsner's. Our batting average is,—I cannot give you the exact figures, but it is high. Every now and then we miss a carcinoma; but what we are saying is that if you have radiologic evidence of an ulcer, if you study that case carefully, and its clinical response to therapy, you can come up with the accurate diagnosis in 95 per cent of the cases, in my opinion. Every now and then, of course, you are going to miss a carcinoma that cannot be demonstrated by any means. Those are the ones you burn your fingers on.

But that is not the problem we are talking about here. We are talking about the ulcer that you demonstrate by x-ray: Is it benign or is it malignant? My experience is that of Dr. Kirsner's.

Moderator DeBakey: *To return a moment to gastroscopy, do you use it in your diagnostic work, frequently?*

Dr. Ruffin: In any gastric ulcer, yes.

Moderator DeBakey: *Well, let me ask you, what is the purpose of it?*

Dr. Ruffin: We always use any diagnostic procedure which does not harm the patient if it adds information of value. If you have a debilitated patient, or one who has an extreme kyphosis, and the procedure is dangerous, of course we will not do gastroscopy. But, to me, the observation of a sharp and clear-cut margin of an ulcer, with no inflammation around it, no induration and normal peristaltic waves, is pretty good evidence that this is a benign ulcer.

I am perfectly willing to admit that there are a number of carcinomas in situ in which the mucosa is intact. You are bound to miss those. I am talking about benign gastric ulcer. I think the procedure is extremely valuable.

Moderator DeBakey: *You feel that it provides you sufficient information concerning all phases of gastric ulcer that has been diagnosed by radiologic means?*

Dr. Ruffin: If the condition of the patient permits, and most of them do.

Moderator DeBakey: *In what proportion?*

Dr. Ruffin: I should say 75 or 80 per cent.

Moderator DeBakey: *Let me ask you, what are the factors that complicate the procedure?*

Dr. Ruffin: None, in my experience. I have done three or four thousand without an accident or a fatality.

Moderator DeBakey: *How about you, Dr. Kirsner?*

Dr. Kirsner: I have been doing gastroscopies now, I think, since 1940.

Dr. Ruffin: I beat you, I started in 1937.

Dr. Kirsner: And we have had, in that time, I think, three perforations in the esophagus. In two instances the accident happened one morning, with a special gastroscope; curiously enough, the same instrument which had produced complications elsewhere.

Moderator DeBakey: Time is running short. I would like to take some of these questions that have been submitted. The first question, I think, is a good question: *In uncomplicated gastric ulcer, how long should medical treatment be continued before we go into surgery?*

Dr. Ruffin: I do not think you can put it at any arbitrary figure in days or weeks. If the ulcer is healing progressively, week by week, and if four weeks elapse and the ulcer is still present but with progressive healing, why, wait another week. Then you can say, there is a point beyond which you would not wait, and of course there is. But, to arbitrarily say three weeks, four weeks, or five weeks, or six weeks, I think is a mistake. It depends upon the clinical course of the patient and the evidence of healing, both radiologically and gastroscopically.

Dr. Kirsner: I would agree. I was on a panel once when a surgeon stated that all gastric ulcers not healing in two weeks should be regarded as malignant. I really was quite surprised at that comment, because, as Dr. Ruffin has pointed out, many gastric ulcers take more than six and eight weeks and longer for complete healing. There is, of course, no scientific evidence in support of the surgeon's opinion.

Dr. Lischer: The only trouble is, some of them go on and persist for years. Also some malignant gastric ulcers give clinical and radiologic evidence of temporary healing.

Dr. Sanders: I think our position is about the same. I believe those patients with severe symptoms and definite penetrating ulcers should have preoperative preparation for a few days, then surgery. I also believe those patients with symptoms which are not so severe should have surgical operation withheld until the internist has tried medical treatment, whether it be three, five, or eight weeks. As demonstrated by the slide, we waited eight weeks, six months, and then a year, and the ulcer was gone. But for the patient who shows no healing during the first few weeks, we should proceed to operate.

Moderator DeBakey: *The next question is: Discuss the relative economics of medical versus surgical treatment of cancerous ulcer.*

Dr. Kirsner: This is a good question and an important problem. Which type of therapy will bring the patient more quickly to a point of rehabilitation and a useful life? I think we could debate this question at some length. Maybe I am idealistic, but I think that what is good for the patient should not be a matter of dollars and cents. It should be a matter of medical knowledge of what is good for his health. I admit that I work in an institution where that approach is possible. Maybe I am not practical. But I think an underlying point is implied here in this question,—what do you do with gastric ulcer that just does not heal? I think both Dr. Ruffin and I agree that, regardless of considerations of differential diagnosis, if a particular ulcer does not respond to adequate medical management that person perhaps ought to be treated by surgery for several reasons, including the economics.

Moderator DeBakey: Our time is just about up. There are quite a few questions that remain here. Would the audience like to stay and finish, say, about ten minutes? All right, then, we will go on.

This question is: What is your advice to a physician in a metropolitan area of 10,000 or less, in handling patients with a lesser curvature ulcer?

Dr. Kirsner: I think these patients ought to be given the benefit of the best possible medical observation and attention, combined with the best possible surgical consultation and attention. If that physician is unable to provide the proper medical attention, then he has one or two choices: He can either turn that patient over to some locality where that skill can be obtained, or, if that is not possible, it would be better to have the patient operated upon. However, I would point out that in that type of situation, I also would wish to be very sure about the capability of the surgeon as well as of the internist.

Dr. Lischer: I think the most important thing in that situation is the diagnostic side. In other words to be sure that the ulcer is healing or has healed. The direction of the medical management might be continued by the physician in a town of 10,000 during the interim of three or four weeks, which has been set aside to see whether the ulcer heals. If on returning to someone expert in radiologic examination the ulcer is not healed, then that patient is a candidate for surgery.

Moderator DeBakey: *The next question, Dr. Kirsner, is addressed to you. Discuss the healing of carcinomatous ulcers.*

Dr. Kirsner: I think there has been a good deal of misinterpretation about this matter of healing carcinomatous ulcers. The original proponents of this idea and those who presented the evidence had in mind, first of all, complete healing, not partial healing. Our responsibility must be in achieving complete healing; that does not occur very often. Such cases are spectacular but they are not common.

Moderator DeBakey: *You mean it does not happen that a cancerous ulcer ever heals completely?*

Dr. Kirsner: I am sorry I did not make myself clear. I think there may be complete temporary healing, of a carcinomatous ulcer, but I do not think that it occurs with the frequency emphasized by some physicians.

Moderator DeBakey: Anybody else?
Dr. Sanders, the next question is addressed

to you. What is the percentage of mortality in the 500 gastrectomies with fully five years of survival? Were not 100 carcinomatous?

Dr. Sanders: That is a good question, but I do not have the answer because I do not have a follow-up for all cases at the present time. However, it has been my experience in handling surgical cases of resection that over a period of years the mortality rate has gradually decreased. Those of you who have practiced since the early days know we did not have the preoperative preparation we have now. Antibiotics and other preliminary preparations for surgery which we now use have lowered the mortality rate.

We had a mortality rate of 5 or 6 per cent for a good while, but the mortality has been slightly less than 2 per cent with our last 200 or 300 cases. The results after resection of the gastric ulcers have been remarkably good and equal those of the duodenal ulcers, which have a fine longevity record. The cases that proved to be carcinomatous, when resected early, as shown in some of these slides, have lived long. We have two or three patients who have lived more than ten years after operation and are still well. Some of these cancer cases are living longer because they came to operation early, but if surgery is withheld until the diagnosis is complete, and you know it is a cancer, the life-span may be very short.

Dr. Kirsner: May I speak to that? I think there is a factor here that has not been mentioned at all which is very important in the survival of patients with gastric carcinoma, namely, the biologic nature of the tumor. I agree that surgery is the best treatment for carcinoma or suspicion of carcinoma, as Dr. Sanders has pointed out, but other factors influence the survival of patients with gastric carcinoma, especially the factor of biologic predeterminism. Prolonged survival may be possible in some cases despite apparent delay in diagnosis. Gastroscopically an estimate of biologic type may be possible by the gross classification of Borrmann.

I think the biologic nature of tumors has an important effect on survival rate, in addition to the tremendously excellent skill of the surgeon.

Dr. Sanders: It is very difficult to tell.

Dr. Kirsner: That is how the diagnosis is made, but it still does not alter the response.

Moderator DeBakey: We still have some questions and five minutes left. *One is this question that is addressed to the surgeons and, presumably, by a good medical man. What percentage of young patients have had adequate medical workup prior to enlisting surgery?*

Dr. Lischer: I think I can answer that by saying 100 per cent.

Moderator DeBakey: *That is, those that are not subject to further study.*

Dr. Lischer: Yes. I might also add, by the same token, there are lots of gastric ulcers that we do not see.

Dr. Sanders: I might add just one word by giving you a time element. In my early days I had practically no help. I was almost the country doctor; I had to do all the diagnostic work and make my own decisions. But as time has passed on and we have good internists available, we work with them, listen to them, and our diagnostic phase has improved.

Moderator DeBakey: *What percentage of patients who have had resection for a benign lesion eventually have had neoplasm?*

Dr. Lischer: I think I stated earlier that it is very rare for gastric carcinoma to develop in a remnant of the stomach following subtotal gastrectomy for benign ulcer. Does that answer the question?

Moderator DeBakey: Nobody has suggested the resection of benign ulcers as a prophylactic measure.

Dr. Lischer: Another reason that it is not a prophylactic measure, I think the members of this Panel agree, is that a benign gastric ulcer does not very often develop into a malignant ulcer. It is either benign or malignant in the beginning. We all agree on that.

Moderator DeBakey: *Would you resect a gastric ulcer, which had resulted from steroid therapy?*

Dr. Lischer: I would like to know, "what was the reason for the steroid therapy?" I cannot answer that question. I think there may be indications for surgery such as perforation or bleeding, but in general, withdrawal of the therapy, or the over-all reason for the therapy would be more important.

Dr. Ruffin: We often use steroid therapy in ulcerative colitis, or in patients with arthritis, and not infrequently those people who

will perforate or bleed have an acute ulcer. I think the answer is obviously no. Of course, if there is perforation, you are going to have to do a resection, but otherwise no.

Moderator DeBakey: *Are large gastric ulcers, in poor risk patients, worth resection?*

Dr. Lischer: The really large gastric ulcer in my experience has been in elderly, undernourished, poor risk patients, and also, as I stated, these have been benign. It does not mean that they are all benign, but in the patient who is a poor risk, who is old, who has a huge gastric ulcer in which, if malignant, you would have to resect the pancreas or a lobe of the liver, a portion of the colon, or spleen to get the cancer out, it behooves you to prove whether it is benign or malignant. If it is benign, you have done such a patient a terrible injustice by multiple-organ resection. It usually is possible to demonstrate this adequately by the frozen section technic at the time of operation. In an ulcer in which you suspect it is benign, in spite of its huge size, I would convert that situation into a simple one by leaving the ulcer in place, and it is usually the pancreas. The whole thickness of the wall of the stomach is gone, so you have the pancreas really forming the crater of the ulcer. You can remove the ulcer around the edge and then go ahead with the gastric resection, or perhaps, an even simpler procedure, if the patient's condition is extremely bad.

Dr. Sanders: I would like to amplify that just a little. If you will go back with me thirty-five years, Sir Berkeley Moynihan, of England, one of our great surgeons, finest orators and writers, spoke in Montreal many years ago on this same problem. A very large perforating gastric ulcer often has for its base only the pancreas or liver and no gastric mucosa. Dr. Moynihan advocated wide gastroenterostomy opposite the ulcer. If the patient was in poor condition and could not stand anything other than a minor operation, he did a gastroenterostomy and added jejunostomy for feeding purposes for a short time, and allowed the patient to get in better condition before anything further was done. He found they nearly all recovered and required no further treatment.

I adopted that method many years ago, treated several very large gastric ulcers in like manner, and the patients were completely relieved. More than 30 years ago, after such treatment, a patient lived at least 15 years with no further trouble. She died from pneumonia, and probably would still be alive if we had had antibiotics in those days.

Moderator DeBakey: I do not think we have time to comment on these except very briefly: *How can one get useful information from gastroscopy when it is usually impossible to tell ulcer from cancer, at time of surgery? And, the other, What are follow-up major methods by which you are able to make the diagnosis 95 per cent?*

Dr. Kirsner: I think Dr. Schindler has discussed the matter of peculiar advantages of the diagnostic quality of the examination he helped to introduce. I do not think the surgeon's hand is always the best way to diagnose carcinoma of the stomach. Unfortunately, we have had patients in whom the surgeon at the operating table could not feel the carcinoma that had been suspected clinically and was diagnosed subsequently, histologically.

Now, as to the second question, they represent a combination of x-ray, gastroscopy, cytology, gastric analysis, stool examinations, and other clinical data; the patients are in the hospital; the examinations are repeated at frequent appropriate intervals.

Dr. Ruffin: Response to therapy.

Dr. Kirsner: And response to therapy.

Moderator DeBakey: Dr. Sanders, I think your trouble has been that you have not used the gastroscope after you have taken the lesion out. After you take out the lesion, you can look at it with the gastroscope.

Dr. Sanders: Thank you for that suggestion, but I do not have enough money to buy one.

Moderator DeBakey: Our time is up, and I want to thank the Panel members.

UP TO THE PRESENT

Drugs Affecting the Autonomic Nervous System: Part II. Clinical Application in Gastrointestinal Disorders

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Evaluation of Anticholinergic Drugs

THE EVALUATION OF ANTICHOLINERGIC DRUGS presents many problems. These have been discussed in detail previously.[35,41,42] Although experimental animals can be used for the initial screening, human pharmacologic studies are necessary for definitive evaluation. The development of satisfactory technics for the measurement of pharmacologic activity of a drug constitutes one of the chief difficulties.

The major action of the anticholinergic compounds consists of interference with the transmission of nerve impulses mediated through acetylcholine and thereby inhibits gastric secretion and gastrointestinal motility. Most of the drugs, in the usual dosage, are active at the postganglionic effector site. The quaternary amines, however, and to a lesser extent the tertiary amines, produce some degree of ganglionic blockade when given in a high dosage.[31]

Any drug proposed for the treatment of peptic ulcer may be evaluated satisfactorily in the following manner. One should determine its effect upon, (1) gastrointestinal motility; (2) gastric secretion; (3) the acute phase of the disease; and (4) the natural history of the disease. The presence and severity of side effects also must be evaluated.

The evaluation of these drugs in the treatment of diseases of the biliary tract or pancreas is even more difficult. While the effect of the drug upon pancreatic secretion or spasm in the ducts obviously is important, this is difficult to measure and one must rely chiefly upon the clinical response of the patient. In biliary tract diseases one attempts to evaluate the relief of spasm, as the antisecretory factor is unimportant.

An anticholinergic drug is evaluated chiefly in regard to its effect upon motility in disturbances of the small bowel and colon, since the antisecretory factor is unimportant, so far as is known. Again, one must rely upon the clinical response of the patient to the drug. Often where symptoms are thought to be due to spasm, there is little evidence that this is so. Probably the difficulty is not one of spasm but rather of asynchrony of peristalsis, and the fact that a drug relieves the symptoms does not necessarily mean that it has relieved spasm.[43,44] Actually there is no real agreement as to what is desired in an antispasmodic drug.[45]

Effect Upon Gastrointestinal Motility. The effect of a drug upon gastrointestinal motility may be studied either radiographically or by balloon kymography. The radiologic method employing a barium motor meal is the simpler and more generally used. This method can be employed in the evaluation of drugs given both orally and parenterally.[33,35,38] The gastrointestinal tract is examined by fluoroscopy, and by x-ray studies following ingestion of a barium meal, and at intervals of 1, 2, 4 and 6 hours. The procedure is then repeated after administration of the drug under consideration. The effect of the drug upon gastric motility and evacuation and the progress of the motor meal through the bowel is observed. Although this is a relatively crude technic, it is

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easily performed and is usually without discomfort to the patient.

In balloon kymography, a tube with one or more rubber balloons is introduced into the lumen of the gut and the open end of the tube is connected to a pressure recording device.[41] Although "motility" can be studied with this technic, there are many deficiencies in this system of recording.[46] To circumvent these difficulties Quigley has suggested the use of highly sensitive pressure-detecting devices which are connected to small, open-tipped tubes and then inserted into the lumen of the gastrointestinal tract. Intra-lumenal pressures are then recorded accurately.[47] This technic has been used primarily in studying the distal colon and, to a limited degree, the upper gastrointestinal tract.[48,49]

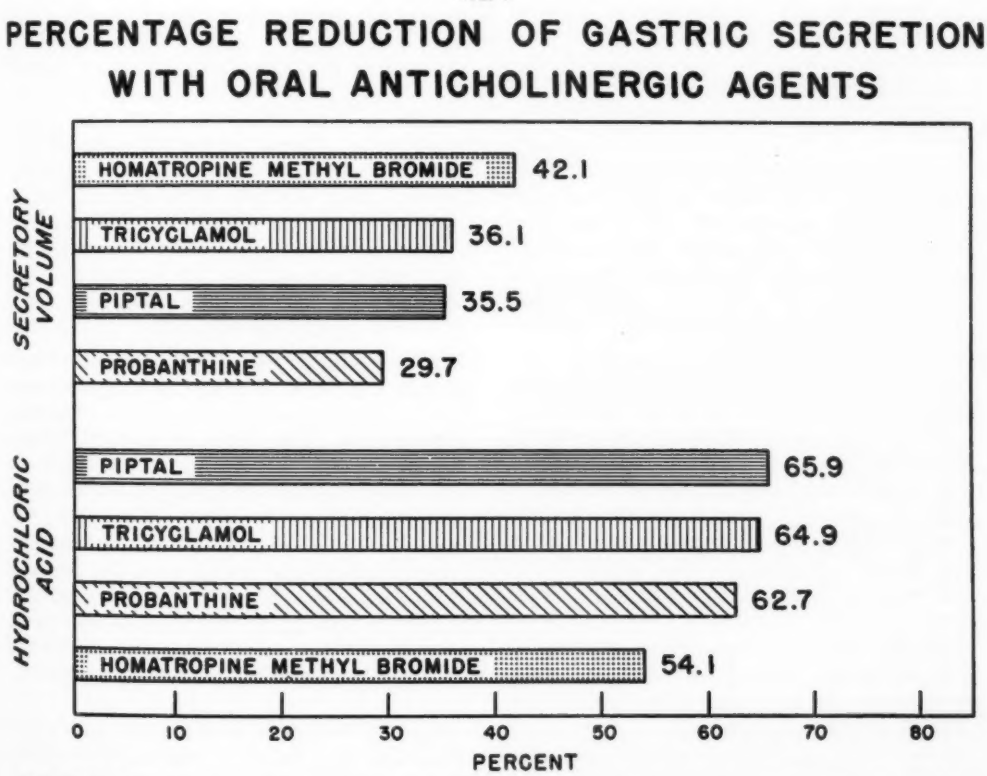
The depressant effect of anticholinergic drugs upon gastrointestinal motility can usually be demonstrtaed using either technic. The belladonna alkaloids, in the usual doses, may have some motor depressant effect upon the small bowel.[50,51] With higher doses, delay in gastric emptying and in small bowel transit may be observed.[40]

The synthetic tertiary amines have variable activity. Most of these are musculotropic spasmolytics, and little antispasmodic activity can be demonstrated in the human subject.[20] However, both Bentyl and Centrine have been shown to have some motor depressant effect.[40,48,52]

The quaternary amines are highly effective in depressing motor activity, especially when administered parenterally.

Antisecretory Effect. A variety of technics have been employed to evaluate the antisecretory effects of drugs. For the most part, these consist of measuring the depression of basal gastric secretion. The fasting gastric contents are aspirated and discarded, and the stomach is emptied as completely as possible

FIG. 7



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either continuously or at 15 minute intervals for a given period of time. The total volume and the amount of free hydrochloric acid are measured before and after administration of the drug, and the inhibitory effect of the drug is expressed as a percentage of the control value[35] (Fig. 7). There are a number of errors in this approach. These include the addition of saliva to the gastric contents, the loss of gastric juice through the pylorus, and incomplete aspiration of the stomach. Reverse peristalsis with regurgitation of bile into the stomach can also decrease the acidity. Likewise, psychologic factors relating to the passage of the tube and extraneous stimuli affecting gastric secretion may influence the results. Only patients with high secretory rates should be employed for these studies. A sufficient number of studies must be carried out with each drug studied to obtain statistically valid data. Although most workers have used the one hour basal gastric secretion test, there is some evidence to indicate that a longer period may be desirable.[53] As additional studies accumulate, it is becoming more apparent that repeated controls are necessary to determine the normal secretory response of any patient before administering an antisecretory drug.[54]

There are differences in interpretation of the data obtained from studies of gastric secretion. The duration of suppression of gastric acidity to pH 4.5 or higher as the criterion of the significant antisecretory effect has been used by some.[42,55] Others feel that no significance should be attributed to less than 25 per cent inhibition of acidity or secretory volume.[41] Still others employ anacidity as an index of significant effect.[34]

Effect Upon the Acute Phase of the Disease. While the effect of a drug upon motility and secretion is extremely important in its evaluation, of equal or even greater importance is the effect of the drug upon the disease itself. It is realized, of course, that such a study is for the most part subjective, as there are few satisfactory objective measurements of improvement or healing of the disease process, especially in duodenal ulcer.

For this reason a "double-blind" study is necessary for the clinical evaluation of a drug employed in the treatment of a disease which is characterized by spontaneous remissions and relapses. The essentials of such a study consist of seven fundamental principles: (1) similar groups of patients; (2) a sufficiently large number of patients in each group; (3) identical treatment of each group with one exception, drug versus placebo; (4) a "double-blind" study with neither patient nor investigator knowing the nature of the medications being used; (5) a daily record of symptoms kept by the patient; (6) an adequate period of continuous therapy; and (7) statistical analysis of the results.[56,57]

Natural History of the Disease. Although there have been numerous glowing reports in the literature concerning the anticholinergic drugs, many of these are open to criticism as they were clinical impressions only and ignored the natural history of the disease. Controlled studies were not employed, and improvement following the administration of a drug was attributed to the drug itself without giving due consideration to other factors such as diet, hospitalization, and the all-important psychogenic factor. Such studies are of questionable value in the assessment of a drug.

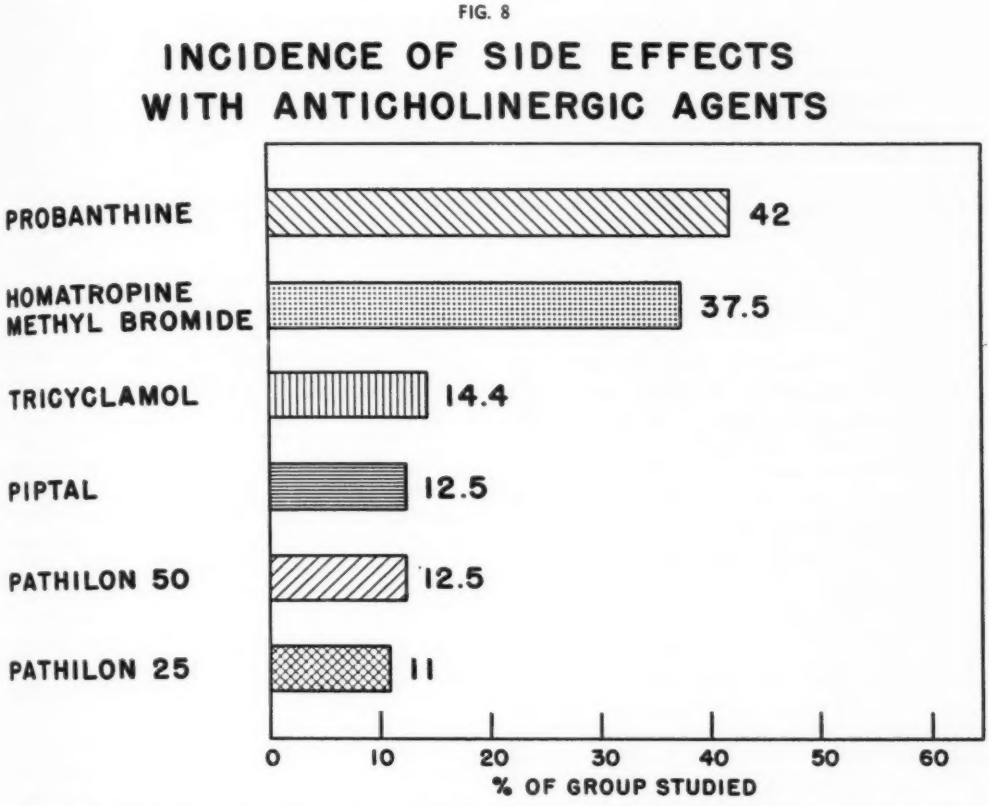
Side Effects. Naturally the side effects of a drug are important in clinical evaluation. The most useful drug is that which produces the maximal desirable physiologic effects with a minimum of undesirable side effects. Obviously, a drug whose side effects are worse than the symptoms arising from the disease under treatment is of no value. For the most part effects of the newer drugs are milder in comparison to their pharmacologic activity. In general, those of the quaternary amines are less than those noted with the tertiary amines (Fig. 8).

Clinical Application

In general the symptoms which one experiences as a result of disease of the gastrointestinal tract are due to alterations in motility, although in some instances abnormal secretion may be an important factor. Therefore, the administration of drugs for the relief of symptoms, whether due to a functional disturbance or to organic disease, is designed primarily to restore normal motility and to a lesser extent secretion. By far the majority of symptoms arise from hypermotility and hypersecretion, although in some cases symptoms may result from decreased motility or secretion.

For convenience the clinical application of drugs affecting the autonomic nervous system may be discussed under five separate head-

FIG. 8



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ings: (1) adrenergic drugs; (2) adrenergic blocking agents; (3) cholinergic drugs; (4) ganglionic blocking agents; and (5) cholinergic blocking agents.

Adrenergic Drugs. Theoretically these drugs should be of value in the treatment of gastrointestinal disorders by inhibiting motor and secretory activity. Actually they have little effect and from a practical standpoint are of no clinical value. For this reason adrenalin, ephedrine and similar drugs are rarely used in gastrointestinal disturbances.

Adrenergic Blocking Agents. The recently introduced tranquilizing drug, reserpine, stimulates gastric secretion and gastrointestinal motility.[58] For these reasons, this drug is contraindicated in patients having a peptic ulcer, or at least should be used with caution.[59] It has been reported that the administration of Dibenamine relieved cardiospasm,[13] but this has not been confirmed.[14] Certainly the adrenergic blocking agents have no particular role in the treatment of gastrointestinal disturbances.

Cholinergic Drugs. There are many conditions in which an increase in tone or peristaltic activity is the objective of treatment. Since this is the pharmacologic action of the cholinergic drugs, theoretically they should be of value in the treatment of such conditions as cardiospasm with dilatation of the esophagus, dilatation of the stomach following operation or anticholinergic drugs, gastric retention not due to organic obstruction, adynamic ileus regardless of cause, and megacolon.

Probably the most effective member of this group is Urecholine. In patients whose stomachs are completely paralyzed by an anticholinergic drug, Urecholine will induce peristaltic activity and cause complete gastric emptying within a period of 20 to 30 minutes. This drug is likewise extremely effective

in restoring the tone of a dilated stomach when due to causes other than organic pyloric obstruction.[60]

In our experience, cholinergic drugs are of no value in the treatment of cardiospasm, dilatation of the small bowel, or megacolon. Actually they may precipitate substernal distress in patients having cardiospasm. Although they cause some increase in gastric and pancreatic secretion, this particular effect has no clinical application and constitutes a contraindication in patients having peptic ulcer or pancreatitis.

Ganglionic Blocking Agents. Although some of the ganglionic blocking agents have been used in the treatment of gastrointestinal disturbances, they actually have proved of little value and are rarely employed today.

Cholinergic Blocking Agents. By far the most valuable drugs from a clinical standpoint are the cholinergic blocking agents. Certainly, they represent a real addition to drug therapy in gastroenterology and have given the physician highly effective tools with which to work. It is true that belladonna alkaloids are still widely used, but their effect is hardly comparable to that of the quaternary amines. In the usual clinical dosage the belladonna alkaloids probably affect secretion little or not at all and their chief benefit seems to be the reduction in spasm and tone in functional gastrointestinal disturbances.[50,51] With the newer delayed action preparations, definite antisecretory activity can be achieved by using higher dosage.[40,61] In doses necessary for antisecretory activity, however, side effects are rather frequent.

The synthetic tertiary amines have probably the least well-defined use. While these drugs have a musculotropic action in animals, by and large this group of compounds has been disappointing. Admittedly most of these drugs can be given without producing severe side effects, but the question has been raised as to whether they produce any effect at all. If they have any usefulness, it would appear to be in those patients in whom a mild so-called spasmolytic drug is desirable.

Of the cholinergic blocking agents available today, the quaternary amines have the greatest clinical application and have been used in the treatment of a variety of disorders of the gastrointestinal tract. The most important use is in the treatment of peptic ulcer.

The pharmacologic effects of the quaternary amines, namely decrease in motility and reduction of acidity, should bring about ideal conditions in the stomach for the healing of an ulcer. Certainly, healing anywhere in the body is enhanced by placing the part at rest and removing irritating substances. The goal of treatment in the ulcer patient is to place the stomach completely at rest and to suppress or neutralize hydrochloric acid. The perfect drug would be the one whose administration is followed by these effects, without side effects; unfortunately such a drug is not available today. Nevertheless, the quaternary amines have proved valuable in the treatment of ulcer.

Without question relief of ulcer pain is the outstanding clinical effect of the quaternary amines. Potent anticholinergic drugs given intravenously result in dramatic and almost immediate relief of visceral pain, arising from a duodenal or gastric ulcer.[62-64] When administered orally, this effect is less striking, but nevertheless has proved extremely useful in controlling ulcer distress. The pain arising from irritation of the somatic nerves in a perforated walled-off ulcer is usually not affected by the anticholinergic drugs. For this reason visceral pain experienced in the epigastrium may be completely relieved while somatic pain in the back or portions of the chest wall persists. Occasionally the pain in the back or chest wall is due to somatic overflow from visceral stimulation, and this pain is likewise relieved by anticholinergic drugs.[65]

With increasing experience the indications for the anticholinergic drugs have become more clearly defined.[64,66] The quaternary amines are not necessary in all patients having an ulcer. The mild cases do well on conventional therapy without anticholinergic drugs. For the moderately ill patient whose symptoms persist in spite of good ambulatory medical management, the addition of a potent anticholinergic drug may be followed by gratifying symptomatic relief, and is definitely indicated.

All patients with ulcer who do not respond to a program of management as outlined above should be hospitalized and given anticholinergic drugs parenterally, in addition to conventional therapy. A practical method of parenteral administration is to give an anticholinergic drug intramuscularly every six

hours for three to five days. In patients having severe pain, an initial intravenous dose is desirable.

While there is general agreement that the cholinergic blocking agents are of great value in the acute phase, their status in the interim management of ulcer is not as clearly established.[64,66] Only a few studies have been carried out to determine the effect of prolonged administration of anticholinergic drugs on the natural history of the disease.[56,57,67] Patients who take anticholinergic drugs are symptomatically improved and have fewer recurrences than those on conventional management.[56,57] The incidence of complication and the necessity for surgery, however, are not altered. Although symptomatic improvement usually follows the use of these agents, they do not alter the natural history of the disease.

While the major usefulness of the anticholinergic drugs has been in the treatment of peptic ulcer, these drugs have been employed in other diseases of the gastrointestinal tract. They have proved of value in the treatment of acute pancreatitis and some observers have found them useful in the management of chronic relapsing pancreatitis.[68] This beneficial effect may be accomplished in two ways: (1) by reducing the normal stimulus to pancreatic secretion, namely, hydrochloric acid, and (2) by actual diminution of pancreatic secretion itself. In the acute case the drug should be given parenterally, and in our experience has been very effective. There is some question as to whether the prolonged oral administration of these drugs actually decreases the number and severity of the recurrences.

The drugs have been used in various disturbances of the small bowel and colon. It has been our observation that these drugs have been of little value in regional enteritis and in ulcerative colitis. Although the quaternary amines have been advocated for various functional disturbances of the gastrointestinal tract, it is our feeling that such treatment merely subjects the patient to unnecessary expense and should be frowned upon. The belladonna alkaloids in combination with sedation are frequently prescribed for patients with the irritable bowel syndrome.

Summary

A clear understanding of the anatomy and physiology of the autonomic nervous system is essential to the intelligent use of autonomic drugs affecting the gastrointestinal tract. Classification of drugs according to their pharmacologic activity is likewise essential for the intelligent use of these drugs. This phase of the problem has been reviewed in Part I.

The various methods for evaluating the effect of anticholinergic drugs have been discussed. The clinical application of autonomic acting drugs to the various diseases of the gastrointestinal tract has been reviewed in Part II.

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EDITORIALS

THE TREATED TUBERCULOUS LESION: ITS PATHOLOGY AND BACTERIOLOGY

Antibiotics and chemotherapy have altered the clinical course of many diseases including tuberculosis. In a chronic disease, such as this, one anticipates that the morphologic picture might well be altered and such is proven to be the case. Furthermore, there has been much speculation about *Myco. tuberculosis* still found in the tissue of resected lungs after specific therapy, its virulence and sluggish cultural characteristics. Resected pulmonary tissue offers excellent material for study.

Loring and Vandiviere[1] have reviewed the morphologic changes which numerous investigators have written about since the advent of antituberculosis therapy and consider these in light of their pathogenesis. The writers say that workers in the field have found in patients treated by streptomycin a different pathologic pattern than in those treated by isoniazid, and agree that para-amino-salicylic acid does not influence the picture.

Streptomycin may alter the classical miliary lesion by complete fibrosis without evidence of pre-existing tuberculosis. If caseation does remain there is an "exaggeration of surrounding collagen." However, the bacillus is demonstrable in both types of lesions. Larger lesions show less inflammatory reaction, illustrated by alveoli empty of exudate and a thinner capsule about the focus; bronchiolar disease is less and shows healing of its junction with cavitation. Cavities are little affected, showing areas of necrosis demarcated by granulation tissue and epithelioid cells.

Isoniazid causes a differing pattern of reaction in healing. Giant cells, rather more like the foreign body type than the Langhans' type, are often found not in areas of tubercle formation but distant in mucus plugs in bronchioles, or isolated in the collagenous tissue. They contain lipid inclusions which, along with collections of xanthoma cells, are positive to fat stains. Calcified bodies may be found. Some granular noncaseous lesions with lymphocytic infiltration and surrounding epithelioid cells suggest the lesion of Boeck's sarcoid. There is a marked increase in collagen bundles. In contrast to the condition of the walls of cavities in those treated with streptomycin, a good percentage of the cavities show a thin hyperemic wall consisting of fibrocytes without epithelialization, except for a short distance of bronchiolar epithelial ingrowth if the cavity communicates with the bronchial tree. Some cavities contain fluid.

These morphologic alterations to the organisms no doubt represent a heightened resistance of the host and a direct effect of the drug on the bacillus. Studies by others seem to indicate that streptomycin is bacteriostatic, effective mainly in the phase of multiplication and on extracellular organisms with little penetration into caseous areas or cavities. Isoniazid appears to be bacteriocidal, acts on intracellular organisms and is able to penetrate into the lesions. The effect on the early lesion may well mean that specific therapy having "paralyzed" the organism, body defenses can take over and more or less abort the process. The type and distribution of cellular reaction in the lesion altered by isoniazid probably represent, in the authors' minds, reactions to the products of destroyed organisms. (This is an application of the well-known variation in reaction to the lipid and protein fractions as shown years ago.) They emphasize the cavitary healing, rarely seen in tuberculosis before the days of chemotherapy, the host's defenses now being permitted to act to the utmost.

In a second paper these authors[2] consider the tubercle bacilli in relationship to treated disease,—the possible sterilization of tissue by drugs and/or the host's reaction, and modification of the organism by treatment. Even before the days of chemotherapy for tuberculosis, it was known that the *Myco. tuberculosis* might be found in the tissue but still seemed to be uncultivable. The present studies involved both the culturing of organisms and the demonstration of resistance to drugs.

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Various types of cavities were studied from this standpoint.

The open cavity permitting exchange in air and fluids with the bronchial tract apparently allows the organism to maintain its usual metabolic activity, and thus organisms were cultured as usual in 6 to 8 weeks. Such a cavity also would permit a variability in concentration of the specific drugs, and it would be expected that the organisms in an open cavity might become resistant to the drugs. Such was the case.

In closed cavities the circumstances are not ideal for growth and multiplication of organisms, and host antibodies may also play a part in this. The bacteria being in a state of depressed metabolic activity may not react to the specific drugs. When cultured such organisms need time to readjust their metabolic depression. Thus, none grew in the usual 6 to 8 week period. Some grew out only after periods of incubation up to 10 months. In end-stage or healed open cavities, those with shiny, clean thin walls, organisms were found in tissues from some but none could be cultured over prolonged periods.

From these two studies the authors raise questions concerning the management of patients. They consider the pros and cons of the surgical removal of end-stage cavities. They wonder if the closed cavities should not be resected earlier. They imply that isoniazid probably should be used early because of its greater effectiveness in localization of the disease. The open cavities commonly contained organisms that quickly grew out on culture and were resistant to drugs, and thus probably represented drug failures at least with reference to the cavity and its organisms.

ANEURYSM OF THE ABDOMINAL AORTA

The remarkable advance in vascular surgery which permits the surgeon to excise an aneurysm of the aorta and to repair the defect by a segment of frozen aorta or by an artificial graft is one of the outstanding accomplishments of surgery. The fact that this can be done is a stimulus to the internist and family physician to be constantly on the lookout for this lesion. This is especially true if the physician responsible for the patient's health recognizes the gloomy prognosis inherent in this lesion. Statistics indicate that death due to rupture may be antcipated in from 63 per cent[1] to 82 per cent[2] of cases. The duration of life after the onset of symptoms usually is to be measured only in months.

Fortunately the surgical attack upon aneurysm of the abdominal aorta has become feasible coincident with the increasing incidence of this lesion. The increased frequency of this manifestation of arteriosclerosis has become one of the penalties of an aging population and is certain to be met still more commonly in the coming years. Aneurysm of the abdominal aorta has become so closely related to old age that some authors have glibly said or implied that the etiology of this lesion is *always* arteriosclerosis. This seems to be borne out by the age incidence in the various series of cases reported in the past decade, in which few aneurysms are reported in the fifties and only an occasional one under 50 years of age. The majority fall into the age limits of 60 to 80 years. The young clinician, to maintain a balanced perspective, should realize that other etiologic factors may play a part in aneurysm of the abdominal aorta, especially in the occasional younger patient suffering from such a lesion. He should be reminded that Kampmeier,[2] in 1936, in 73 cases found only nine above the age of 55 years, and only 13 between 45 and 54 years of age. The age of greatest incidence was in the decade 35 to 44, with 24 cases in this group. Six occurred in the ages of 20 to 24 years. In past years, then, syphilis played a large part in the etiology of aneurysm of the abdominal aorta. It may be well to remind one's self that some day one may encounter such a lesion in a patient of younger years than one has been wont to believe, and that recognition of an etiologic factor other than arteriosclerosis might suggest specific preoperative treatment preparatory to surgical intervention. Syphilitic aneurysms are more likely to arise above the origin of the renal arteries, arteriosclerotic ones below this point.

Enselberg[3] has recently reviewed the clinical picture of aneurysm of the abdominal aorta

1. Estes, J. E., Jr.: Abdominal Aortic Aneurysm: A Study of One Hundred and Two Cases, Circulation 2:258, 1950.
2. Kampmeier, R. H.: Aneurysm of Abdominal Aorta: Study of 73 Cases, Am. J. M. Sc. 192:97, 1936.
3. Enselberg, Charles D.: The Clinical Picture of Aneurysm of the Abdominal Aorta, Ann. Int. Med. 44:1163, 1956.

as has been described by numerous authors in the past. Though not present in all, pain of some type is common, referred to the abdomen in general, or to the lower abdomen, often the left side. Pain in the lower back with at times radiation to the thighs is described by some patients. The diagnosis of renal colic is not uncommonly entertained because of the pain in some instances. Unusual or abnormal pulsation, at times with a recognized tumor, brings some patients to the physician. The most characteristic physical sign is a palpable abdominal mass and especially one showing *expansile* pulsation. The latter may be absent if clots are present in the aneurysm. The evidences of occult bleeding, the constitutional signs of blood loss verified by a falling hematocrit in an old person, should suggest aneurysm of the abdominal aorta, for leakage from the lesion into the retroperitoneal tissues may proceed for some hours before gross rupture and death. By now numbers of patients have been successfully operated upon after bleeding has begun.

Roentgenography often shows calcification in the walls of the aneurysm and may be of diagnostic aid; so too erosion of vertebrae may be suggestive, more likely to occur in the syphilitic variety because of a higher location and probably more forceful pulsation.[2] Aortography is the latest addition to the diagnostic aids in diagnosis and preoperative evaluation.

Abdominal pain in the oldster means not only possible disease of the gastrointestinal or genitourinary tracts, nor does pain in the back point to disease of the spine alone,—in both it may be the signal of aortic disease.

RESIDENT TRAINING IN FARAWAY PLACES

The training of specialists in certain fields of surgery especially has become increasingly hampered during recent years.[1] The lack of staff or ward patients is a serious handicap in graduate training. The intern can learn by observing and assisting at the operation and in the care of the private patient who is the responsibility of the attending surgeon. But before the resident in surgery completes his training he must have had adequate experience in operations on his own responsibility. A number of factors have conspired to handicap adequate resident training in the fields of surgery especially. Except for some of our largest metropolitan hospitals, ward material has been sharply curtailed in many hospitals because of: (1) "good times," that is, little unemployment and good wages permitting private patient status; (2) third party contracts and insurance coverage for hospital and medical expense, often as fringe benefits in industry, providing for the laboring man of low income the attention of a private practitioner; (3) advances in medical science, as the antibiotics and preventive medicine, which may abort disease, or prevent disease and the complications which demand surgical intervention.

These factors, then, have decreased the case material for proper graduate training, especially in some of the surgical specialties which at best did not have a plethora of ward cases except in the large cities.

Recognizing these facts and being especially aware of the need for specialized attention in one out-of-the-way place, Dr. Fritz,[2] president of the Alaska Territorial Medical Association, and apparently an otolaryngologist, has made some interesting suggestions. He comments upon the mass of clinical material in Alaska, especially in the fields of ophthalmology, otolaryngology and thoracic surgery, for which specialized attention is unavailable. Then he proceeds to make a case for the resident in the States, about ready to go into practice, to serve a six-month period in some hospital in Alaska to put the finishing touches on his operative technics by a surgical "field day." Though he can speak intimately of the needs and the opportunities in his own Territory, he suggests that similar opportunities probably could be found on a world-wide scope in distant places and probably in other fields of medicine.

Though several training programs have availed themselves of the Alaskan opportunity, Dr. Fritz is disappointed in the apathy of those he has approached with this idea. His criticism of deans of medical schools in this regard is misdirected to a great extent for, by and large, they dictate little of the policies of graduate training which are left to the chiefs of the services. It is these and the specialty boards who would need to have interest in this proposition, and the latter might consider accepting

1. Editorial. The Changing Pattern in Graduate Education, South. M. J. 48:553, 1955.
2. Fritz, M. H.: Neglected Medical Educational Opportunities in the World of 1956, Northwest Med. 55:583, 1956.

some months of this type of training without the supervision usually required. A man within six months of the end of his training, presuming it had been good, should be ready to "solo" for the technical experience offered him.

From the author's comments, it appears there is equal or greater apathy on the part of residents to leave the country for such an experience. This, if true, is both surprising and disheartening, for it reveals the disappearance of the American heritage of adventure mixed with a gamble which led to the conquering of the western wilds, the building of industrial empires and the development of a new form of democracy. From a similar experience, your editor knows that the young man who does not seize an opportunity such as Dr. Fritz describes, will probably have missed a nugget of time which he would often recall and to which he would refer as the most interesting months of his life. In middle-age when seeing and treating patients has become routine, and the thrill of meeting a new problem has waned in the well-equipped and furnished office of the successful specialist, the memory of an experience in an out-of-the-way place awakened by some item about a patient at hand fans an ember of past adventure and, temporarily, of youth.

25 YEARS AGO

The Effect of the Ingestion of Burdock Root on Normal and Diabetic Individuals*

"*Arctium lappa* or burdock is a coarse biennial weed which grows in Europe, Asia and North America. Early in the nineteenth century, it was observed that the administration of burdock root was beneficial in cases of skin eruptions, gout, rheumatism and calculous complaints. For many centuries it has been utilized in the kitchen of many households and restaurants of the Japanese. There the root is stripped of its bark and the pulp is sliced, boiled, seasoned, and served as a vegetable much as the occidentals serve parsnips and sweet potatoes. Coincidentally it is interesting to observe that the Japanese have a high racial immunity to diabetes. Burdock has enjoyed some reputation as an alterative in constitutional blood diseases. "Burdock tea," designated as Radix Burdanae in Germany, has been regarded as an efficient blood purifier. From 1830 to 1910, burdock was recognized by the United States Pharmacopeia. Culbreth lists its constituents as inulin, a bitter extract, fat, resin, levulose, and cellulose. . . .

"In 1851 Bouchardat observed that levulose was tolerated better by diabetics than glucose, and noted that patients with mild diabetes were aglycosuric when they ate 50 to 100 grams of this monosaccharide per day. Johanson showed that levulose increased the respiratory quotient more rapidly than did glucose, and that the duration of the elevated quotient was also longer. Straus recommended a daily diet of 50 to 100 grams of inulin and observed that favorable therapeutic results followed. He found also that inulin was antiketogenic. . . .

"Krantz and Carr have shown experimentally that in white rats powdered burdock root causes an increased storage of glycogen in the liver; and further that in dogs it is antiketogenic and has a protein-sparing action. . . .

"With the foregoing facts in mind the influence of the administration of powdered burdock root upon diabetic patients was observed. The first problem was the production of a food-stuff sufficiently palatable to be substituted easily for other carbohydrates in the diet. The dried root was powdered, containing sixty per cent of carbohydrate. A batter was made with 90 grams of the powder, 36 grams of butter, water, salt, saccharin, and a few drops of the fluidextract of ginger . . . and baking . . . as cookies, we obtained a cracker. . . .

(In) "three non-diabetic individuals . . . when the burdock diet was fed there was a preliminary decrease of blood sugar followed by a gradual rise to just below the fasting level at the end of three and three-quarters hours. With the meal consisting of carbohydrates other than those in burdock, a curve similar to . . . that of a normal glucose tolerance curve, was obtained.

"A similar experiment was carried out with known diabetic patients. . . . The curves obtained indicate that there is an inhibitory effect of burdock on the hyperglycemia of glucose.

"Following this work, we began the use of burdock root in the form of crackers as above described as a substitution for the carbohydrates in the diets of several diabetic patients. . . . In these cases the dosage of insulin was decreased as burdock was administered. When the blood sugar approached normal the burdock was replaced by other polysaccharides. Immediately there was a marked rise in the blood sugar which returned at once to its former level on replacing the burdock in the diet. This we found to happen in each instance where the foregoing procedure was carried out. In all cases while burdock was being administered there was no glycosuria. However, upon removing the

*Silver, A. A., and Krantz, J. C., Jr.: The Effect of the Ingestion of Burdock Root on Normal and Diabetic Individuals. A Preliminary Report, Ann. Int. Med. 5:274, 1931.

burdock from the diet of diabetic patients and replacing it by other polysaccharides (Uneeda biscuits) glucose appeared in the urine.

Summary

"1. The carbohydrate in burdock root was absorbed and utilized by certain patients with diabetes mellitus.

"2. In the cases reported burdock root seems to exhibit an inhibitory action on the hyperglycemia caused by the common polysaccharides.

"3. Powdered burdock root may be easily administered to patients in the form of palatable crackers.

"4. Mild diabetic patients may be kept at normal blood sugar levels and aglucosuric by the administration in their diets of crackers made from powdered burdock root."

BOOKS RECEIVED

Oral Cancer and Tumors of the Jaws. By George S. Sharp, M.D., Professor of Pathology, School of Dentistry and Assistant Clinical Professor of Surgery, School of Medicine, University of Southern California; Weldon K. Bullock, M.D., Associate Clinical Professor of Pathology, School of Medicine; and John W. Hazlet, D.D.S., Lecturer, Oral Tumor Pathology, School of Dentistry, University of Southern California. 540 pages, illustrated. New York: The Blakiston Division, McGraw-Hill Book Company, Inc., 1956. Price $15.00.

Human Perspiration. By Yas Kuno, M.D., Member of Japan Academy. 385 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1956. Price $9.50.

Treatment of the Child in Emotional Conflict. By Hyman S. Lippman, M.D., Clinical Professor, Department of Psychiatry and Department of Pediatrics, University of Minnesota Medical School. 291 pages. New York: The Blakiston Division of McGraw-Hill Book Company, Inc., 1956. Price $6.00.

Clinical Selections in Dermatology and Mycology. Edited by Frederick Rehm Schmidt, M.D., Associate Professor of Dermatology, Northwestern University Medical School. 487 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1956. Price $10.50.

A Textbook of Pathology. By E. T. Bell, M.D., Emeritus Professor of Pathology, University of Minnesota. Eighth Edition, with 545 illustrations and five color plates, 1003 pages. Philadelphia: Lea & Febiger, 1956. Price $14.50.

Clinical Hematology. By Maxwell M. Wintrobe, M.D., Professor and Head, Department of Medicine and Director, Laboratory for the Study of Hereditary and Metabolic Disorders, University of Utah College of Medicine. Fourth Edition, 236 illustrations and 20 plated, 18 in color, 1136 pages. Philadelphia: Lea and Febiger, 1956. Price $15.00.

The Neurosurgical Alleviation of Parkinsonism. By Irving S. Cooper, M.D., Assistant Professor of Neurologic Surgery, New York University, Bellevue Medical Center. 97 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1956. Price $8.50.

Treatment of Migraine. By John R. Graham, M.D., Chief of Medical Service, Faulkner Hospital, Boston; Instructor in Medicine, Harvard Medical School. 138 pages. Boston: Little, Brown and Company, 1956. Price $4.00.

An Atlas of the Head, Neck and Trunk. By the late Johnson Symington, M.D., F.R.C.S., F.R.S., Professor of Anatomy, the Queen's University, Belfast. A Series of Plates. Springfield, Illinois: Charles C. Thomas, Publisher, 1956. Price: $21.00.

Atlas of Exfoliative Cytology, Supplement I. By George N. Papanicolaou, M.D. Published for the Commonwealth Fund. Cambridge, Massachusetts: Harvard University Press, 1956. Price $4.00.

Food Hygiene. Fourth Report of the Expert Committee on Environmental Sanitation. WHO Technical Report Series, No. 104.

Expert Committee on Professional and Technical Education of Medical and Auxiliary Personnel. Third Report. WHO Technical Report Series, No. 109. New York: Columbia University Press, 1956. Price $0.30.

Expert Committee on Trachoma. Second Report. WHO Technical Report Series, No. 106. New York: Columbia University Press, 1956. Price $0.30.

Chronicle of the World Health Organization. Vol. 10, No. 5, May, 1956. New York: Columbia University Press, 1956. Price $0.30.

A Manual of Practical Obstetrics. By the late O'Donel Browne, M.B., M.A.O., M.A., LITT.D., F.R.C.P.I., F.R.C.O.G., Master, Rotunda Hospital, Dublin; King's Professor of Midwifery, Dublin University. Edited and largely rewritten by J. G. Gallagher, M.D., M.A.O., F.R.C.P.I., M.R.C.O.G. Third Edition, with 203 illustrations, 253 pages. Baltimore: The Williams & Wilkins Company, 1956. Price $7.50.

Annual Epidemiological and Vital Statistics, 1953. World Health Organization, Geneva, 1956. 571 pages. New York: Columbia University Press, 1956. Price $10.00.

The Recovery Room—Immediate Postoperative Management. By Max S. Sadove, M.D., Professor of Surgery (Anesthesiology) and Head, Division of Anesthesiology, and James H. Cross, M.D., Clinical Assistant Professor in Surgery, both at the University of Illinois College of Medicine. 565 pages, illustrated. Philadelphia: W. B. Saunders Company, 1956. Price $12.00.

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Exclusive Publication: Articles offered for publication must be contributed solely to the Southern Medical Journal.

Manuscripts: Manuscripts should be original copy, typewritten, double-spaced, with wide margins. Footnotes and bibliographies should conform to the following style:

1. Doe, J. E.: What You Should Know about It, New England J. Med. 243:435, 1950.

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BOOK REVIEWS

Potassium Metabolism in Health and Disease

Modern Medical Monograph No. 12. By Howard L. Holley, M.D., Department of Medicine, University of Alabama, Medical-Dental Schools, Birmingham, Alabama; and Warner W. Carlson, Ph.D., Department of Biochemistry, University of Alabama, Medical-Dental Schools, Birmingham, Alabama. 131 pages. New York: Grune & Stratton, Inc., 1955. Price: $4.50.

This manual provides a brief discussion of the clinical aspects of disorders of potassium metabolism. Introductory theoretical considerations are pertinent but suffer from the lack of documentation. A limited bibliography is included but the text contains no direct reference to it.

The various problems which one encounters in clinical practice are clearly presented in a brief, somewhat oversimplified manner. However, the difficulty of dealing with such a complex phenomenon as fluid and electrolyte metabolism from the standpoint of only one constitutent is apparent. Some of the illustrative case summaries are so brief that it is difficult to reach valid conclusions regarding the importance of potassium *per se* in the pathogenesis of the clinical states described. However, the iatrogenic aspects of hypopotassemia are clearly apparent. The authors have quite rightly emphasized the lack of precise knowledge which directly relates neuromuscular phenomena to high and low serum concentrations of potassium respectively.

From the standpoint of the recognition and management of the commoner derangements of potassium metabolism this manual should be helpful as a guide to those with limited experience in such matters.

Life Stress and Essential Hypertension

By Stewart Wolf, M.D., Professor and Head, Department of Medicine, University of Oklahoma School of Medicine; Philippe V. Cardon, Jr., M.D., Senior Assistant Surgeon, National Institute of Mental Health; Edward M. Shepard, M.D., Instructor in Medicine, Cornell University Medical College, and Harold G. Wolff, M.D., Professor of Medicine (Neurology), Cornell University Medical College. 245 pages. Baltimore: The Williams and Wilkins Company, 1955. Price: $7.50.

This book is another monument to the breadth of vision of Stewart Wolf and Harold Wolff. It is a carefully documented and beautifully detailed analysis of essential hypertension from many important aspects. Herein are depicted the average run of the nine patients closely observed and, tangled inexorably in unavoidable and overwhelmingly stressful life situations, they become the victims of all consuming essential hypertension. At first escape is possible, but as organic changes supervene the outcome is inevitable.

The authors have stressed the importance of personality strain. Just as successfully, they have studied circulatory dynamics associated with the progression and regression of hypertension.

The discussion of the treatment of hypertensive disease will be disappointing to those who look for an easy out through simple drug therapy. The authors emphasize that education with early adjustment to life situations is the best treatment by prophylaxis while flexibility and reversibility are still present. Drug therapy at best is a palliative stop gap.

This is a fine, sobering, thoughtful book.

Psychology in Nursing

By Wendell W. Cruze, Ph.D., Professor of Psychology, Wilson Teachers College; Visiting Lecturer in Psychology, the Johns Hopkins University; Lecturer in Psychology, Garfield Memorial Hospital School of Nursing, and Lecturer in Psychology, the Lucy Webb Hayes School of Nursing of Sibley Memorial Hospital. With a Foreword by Lucile Petry Leone, Consulting Editor. 494 pages, illustrated. New York: McGraw-Hill Book Company, Inc., 1955. Price: $5.50.

This is an elementary textbook in psychology for students of nursing. It is a straightforward book beginning with a statement about the historical development of psychology as a science. Then, instead of jumping into the icy waters of the study of the nervous system, the author approaches the subject from the point of view of the student nurse, discussing her unique and particular need for knowledge in this area. A chapter on the psychology of efficiency gives specific suggestions for developing the technics of studying under the sometimes trying conditions of dormitory life.

The chapters on the origin and development of the individual are written from the standpoint of genetic psychology. Then follow three chapters on the structure and function of the nervous system. Italics are used consistently to introduce neuro-anatomical terms and the explanatory material is accompanied by well-selected, uncluttered diagrams.

The last half of the book discusses the problems of motivations, emotions and personality development. This material is quite condensed and will be much more acceptable to students if the visual aids listed at the back of the book are used in conjunction with the text. While films or film strips are suggested for all of the chapters, the last half of the book seems to require these more than the earlier chapters. The author closes with an excellent chapter on psychological aspects of nursing chronically ill and aged patients.

Both physicians and nurses have an acute need to understand the motivation of their patients' behavior and of their own roles in constantly changing nurse-patient and doctor-patient relationships.

This is a good textbook and when used with films, it should provide a basis for worthwhile discussion.

Problems in Amoebiasis

By Charles William Rees, Ph.D., Head, Section on Protozoal Diseases, Laboratory of Tropical Diseases, National Microbiological Institute, National Institutes of Health, Bethesda, Maryland. 109 pages.

Springfield, Illinois: Charles C. Thomas, Publisher, 1955. Price: $4.75.

This small volume brings together in a very useful form important recent knowledge concerning the problems in the laboratory and clinic on amoebiasis. It contains brief and well-written sections on the diagnosis of the disease, usefulness of crude cultures and of monoxenic cultures (cultivation of amoeba with a single selected species of bacteria, trypanosome, or minced embryonic tissue). There is also a chapter concerned with chemotherapy and one on clinical problems in amoebiasis. This book is interesting and should be of value to physicians generally.

Subacute Bacterial Endocarditis

By Andrew Kerr, Jr., M.D., Assistant Professor of Medicine, Louisiana State University School of Medicine. American Lecture Series. 314 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1955. Price: $6.50.

This carefully prepared text covers in a very complete form much of the important literature concerning subacute bacterial endocarditis. It is organized in a way so that reference to individual points is convenient. Key references on bacterial, clinical, and therapeutic aspects are given in the text.

This volume provides a source of information on subacute bacterial endocarditis which is more comprehensive than the section in medical textbooks. It fills a real need and should be interesting to every physician.

Chemotherapy of Tuberculosis. Transactions of the 14th Conference, February, 1955

Prepared and Edited by the Veterans Administration Area Medical Office, Atlanta, and the Department of Medicine and Surgery, Central Office, Washington.

This volume, produced annually by the Veterans Administration in cooperation with the National Tuberculosis Association, provides a comprehensive and detailed report of most of the clinical and laboratory tuberculosis investigation which has been done in the period reviewed. The very complete reporting of the participants' discussions, and the excellent editing and presentation make this a most readable document. This volume could serve as a type for other medical conferences. The breadth and extent of the problems of tuberculosis with which this volume is concerned defy any attempt to summarize. Included in it, however, is information that any physician who is concerned with tuberculosis should have available.

Standard Values in Nutrition and Metabolism

Edited by Errett C. Albritton, M.D., Fry Professor of Physiology, George Washington University. Prepared under the Direction of the Committee on the Handbook of Biological Data, American Institutes of Biological Sciences, the National Research Council. Second Fascicle of a Handbook of Biological Data. 380 pages. Philadelphia: W. B. Saunders Company, 1954. Price: $6.50.

One hundred and sixty tables and diagrams which were compiled and extensively reviewed by more than eight hundred specialists in the United States and abroad are presented in this volume. These tables and diagrams are extensively annotated and bibliographic references are included. The contents may be illustrated by noting the subject headings of the major groupings. These are:

The Nutrients
Nutrients Utilized by Animal Forms
Nutrients Utilized by Plant Forms
Daily Nutrient Allowances (for a wide variety of animals including man)
Diets, Culture Media, for Animal Forms
Culture Media, Fertilizers, for Plant Forms
Nutrient and Energy Values of Foodstuffs and Feedstuffs
Nutrient Functions and Signs of Deficiency and Excess
Pathways of Metabolism
End Products of Metabolism
0_2 Consumption, 0_2 Production: Animal Tissues, Organisms
0_2 Consumption, 0_2 Production: Plant Tissues, Organisms
Energy Exchange
Bibliography
Index

The wide scope of the compilations is best illustrated by noting a few diverse titles of tables:

Zoo Diets: Mammals, Carnivores
Chemical Elements, Functions: Animals
Comparison of Standards of Basal Metabolism: Man
Metabolic Rats: Soil Organisms
Amino Acid Requirements: Insects
Signs of Chemical Element Deficiency: Eight Selected Plants

This volume and the first fascicle entitled "Standard Values in Blood" published in 1952 under the same auspices, and subsequent and projected volumes constitute useful additions to the reference shelf of our libraries.

Modern Nutrition in Health and Disease: Dietotherapy

Edited by Michael G. Wohl, M.D., Chief of Human Nutrition, Division of Biological Chemistry, Hahnemann Medical College and Hospital, Philadelphia, and Robert S. Goodhart, M.D., Scientific Director, the National Vitamin Foundation, Inc., New York. 1,062 pages, 80 illustrations and 127 tables. Philadelphia: Lea and Febiger, 1955.

This is an edited book which treats the broad subject of nutrition as related to medicine. It consists of 37 chapters by 55 contributors. Approximately half of the book deals with nutritional physiology and the remainder with dietotherapy and nutrition in relation to various groups of diseases or physiologic states. The sections on therapeutic diets present the background for the various dietary regimens which are outlined. This book is a reference work which physicians, dentists, medical students and others concerned with human nutrition will find of interest to study. It is not the quick reference type of hospital dietary manual. It will be a valuable addition to the library of any physician.

Continued on page 1092

SOUTHERN MEDICAL NEWS

ALABAMA

Dr. Paul O. Gilliland, a recently retired medical officer, has succeeded Dr. Thomas J. Floyd as public health officer of Houston County. Dr. Floyd, Abbeville, who retired because of poor health, will supervise public health work in Henry County on a part-time basis.

Four orthopedic surgeons have been honored by the Alabama Crippled Children's and the Vocational Rehabilitation Services for over one hundred combined years of charity to the crippled individual. The two Birmingham physicians cited were Dr. John Doke Sherrill, professor of orthopedic surgery at the Medical College of the University of Alabama, and Dr. H. Earle Conwell, now in private practice and associate professor of orthopedic surgery at the Medical College. Dr. W. C. Hannon, state medical consultant for the Crippled Children's and Vocational Rehabilitation Services in Mobile, and Dr. Marcus Skinner, Selma physician and founder of the Marcus Skinner Clinic for correctional surgery and therapy, were also honored. All four are native Alabamians, graduates of the University of Alabama Medical College, and officers in the medical corps during World War I.

ARKANSAS

The following Arkansas doctors have been elected officers in the Veterans of Foreign Wars: A. J. Forestiere, Post Surgeon, Harrisburg; Charles Bailey, Post Surgeon, Greenwood; and Fay B. Millwee, Commander, McCrory.

Dr. F. Walter Carruthers, past president of the Arkansas Orthopedic Society, has been named president-elect of the Mid-Central States Orthopedic Society.

Dr. Harold Hawley joined Dr. Dwight Gray July 1 for practice at Dr. Gray's Clinic in Marianna.

DISTRICT OF COLUMBIA

Dr. Harold J. Jeghers, director, department of medicine, Georgetown University School of Medicine, resigned August 1 to become professor of medicine at the new Seton Hall University School of Medicine in Jersey City, New Jersey. Dr. Jeghers will remain as a consultant in the department of internal medicine at Georgetown.

Dr. James J. Feffer has been elected president of the District Tuberculosis Association and the District Trudeau Society.

Dr. Richard H. Fischer has succeeded Dr. Robert R. Montgomery as president of the George Washington University Medical Society. The other officers are: Dr. Donald H. Leeper, Jr., president-elect; Dr. Helen Gladys Kain, first vice-president; Dr. Frederick Y. Donn, second vice-president; Dr. J. Roscoe Creer, secretary; and Dr. Naomi M. Kanof, treasurer.

Dr. Claudine M. Gay has been installed as president of the Women's Medical Society of the District of Columbia. The others elected to office are Dr. Shirley S. Martin, president-elect; Dr. E. Anne D. Mattern, recording secretary; Dr. Vita R. Jaffe, corresponding secretary; and Dr. Inez E. Wilber, treasurer.

The Jacobi Medical Society has named the following officers: Dr. Monroe J. Romansky, president; Dr. Sydney Ross, president-elect; Dr. Jack L. Derzavis, vice-president; Dr. Melvin O. Goodman, secretary; and Dr. Stanley W. Kirstein, treasurer.

Dr. William T. Spence has been elected president of the newly formed Washington Academy of Neurosurgery. Dr. Jonathan M. Williams will serve as secretary.

Dr. Hugh H. Hussey has succeeded Dr. Harold Jeghers as director of the department of medicine of Georgetown University School of Medicine. Dr. Hussey has been a member of the Georgetown faculty for over 20 years.

Dr. John Hugh Lyons, who has recently relinquished his administrative duties at Emergency Hospital to become Emeritus Chief and Senior Consultant to the department of surgery, was honored with a testimonial dinner.

Dr. Elizabeth S. Kahler has been elected president-elect of the American Medical Women's Association.

Dr. William B. Herbst was elected president of the American Urological Research Foundation.

Dr. Robert E. Moran has been elected to serve a six year membership on the Examining Board of the American Board of Plastic Surgeons.

Dr. Ross T. McIntire, Executive Director of the International College of Surgeons, has been honored by President Eisenhower for his outstanding work in organizing and developing the President's Committee on Employment of the Physically Handicapped.

Dr. Thomas McPherson Brown, professor of medicine of George Washington University School of Medicine, was awarded a citation for outstanding service from the District Commissioners' Committee on Employment of the Physically Handicapped.

Dr. Russell J. Fields was the recipient of an honorary life membership in the American Social Hygiene Association.

Drs. Catherine W. Johnson and John F. J. Clark have been certified by the American Board of Obstetrics and Gynecology.

Dr. Ivan F. Bennett has succeeded Dr. Richard L. Jenkins as chief of psychiatric research in the psychiatry and neurology service of Veterans Administration Central Office.

Dr. Marjorie P. Wilson has been appointed chief of the Veterans Administration residency and internship division in the education service of the Department of Medicine and Surgery.

FLORIDA

Dr. M. S. Hernandez has been certified as a Diplomate by the American Board of Obstetrics and Gynecology.

Dr. DeWitt C. Daughtry has been elected to the National Tuberculosis Association Board of Directors. Dr. Daughtry has served on the Board of Directors of both Dade County and Florida Tuberculosis Associations for several years.

Dr. Irvin Seaman has received certification as a Diplomate by the American Board of Obstetrics.

The Heart Association of Greater Miami has named the following officers: Dr. Jim S. Jewett, president-elect; Dr. Louis Lemberg, vice-president; and Dr. Francis N. Cooke, secretary.

Dr. George F. Schmitt has been elected parliamentarian for the Florida State Association of the National Association of Parliamentarians.

Dr. James H. Ferguson has been elected to membership in the Continental Gynecologic Society.

Dr. Hunter B. Rogers, president of the Dade County Medical Association, presented an engraved plaque to Dean Homer Marsh in honor of the first graduating class from the University of Miami School of Medicine.

Dr. George F. Schmitt has been appointed to the advisory board of the Alumni Association of the Mayo Foundation.

GEORGIA

Dr. Jack C. Norris, councillor from Georgia, reports that on July 20, a group of friends in Atlanta, presented the Golden Anniversary Key, three diamonds, to Dr. Marion C. Pruitt. The key was given in appreciation of Dr. Pruitt's notable record of achievement in proctology, and for his distinguished leadership in the Southern Medical Association.

Dr. W. E. Burdine, Atlanta, has been elected president of the Georgia Association of Nursing Homes.

Dr. Alfred Joseph has received certification by the American Board of Pediatrics.

Dr. J. Gordon Barrow, Atlanta, has been appointed director of the Division of Heart Disease Control for the Georgia Department of Public Health. He will serve as director on a part-time basis.

Dr. Lloyd F. Timberlake will serve as a member of the board of directors of the Atlanta branch of the American Red Cross.

Dr. Dorothy Jaeger-Lee, Atlanta, has been named pediatric consultant with the Division of Maternal and Child Health, Georgia Department of Public Health.

Dr. Thomas N. Guffin has been certified by the American Board of Surgery.

Dr. Forest D. Jones, Atlanta, was recently certified by the American Board of Pediatrics.

Dr. Hal Davison, Atlanta, has been installed as president of the Medical Association of Georgia. Dr. W. Bruce Schaefer, Toccoa, was named president-elect. The other officers are Dr. Carl C. Aven, first vice-president, Dr. Bernard Wolff, second vice-president, and Dr. David Henry Poer, secretary-treasurer. Drs. Eustace Allen and Spencer Kirkland were re-elected delegates to the American Medical Association. Drs. W. R. Dancy, Savannah, and Henry Tift, Macon, will serve as alternate delegates.

Dr. Charles Sterling Jernigan, Sr., was named Georgia's "General Practitioner of the Year." Dr. Jernigan, an 83 year old Sparta physician, began his medical career 59 years ago.

Dr. David Hein has been named to the board of directors of the Jewish Social Service Federation of Atlanta.

Dr. T. F. Sellers, Sr., Atlanta, has been appointed chairman of a commission created by the 1956 Georgia Legislature to make a study of the hospital care for indigent persons who are acutely and chronically ill.

Dr. Guy D. Ayer, Atlanta, and the late Dr. Chris H. Pinson were awarded 50-year certificates by the Medical Association of Georgia.

Dr. Albert J. Kelley, Savannah, has been named chief of obstetrics and gynecology at Memorial Hospital in Chatham County.

Continued on page 50

BOOK REVIEWS

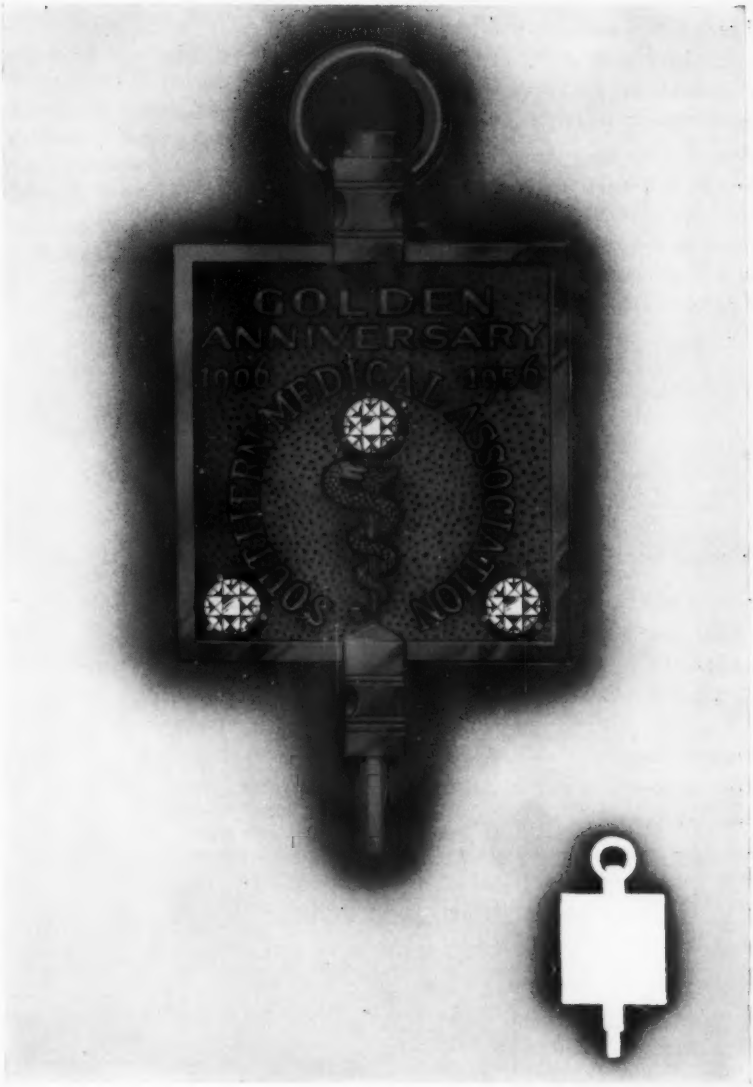
Continued from page 1090

The Blood-Brain Barrier

By Louis Bakay, M.D., Instructor in Surgery, Harvard Medical School, Assistant in Neurosurgery at Massachusetts General Hospital. American Lecture Series. 154 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1956. Price: $5.50.

The pendulum has now completed its swing and it is now *de rigueur* to discuss "the blood-brain barrier." Dr. Bakay presents evidence which summarizes our knowledge on the anatomical location and normal function of this barrier as well as the site and mode of formation of the cerebrospinal fluid. As this book is subtitled "with special regard to the use of radioactive isotopes," this line of investigation is discussed most thoroughly. A comprehensive listing of all of the radioactive isotopes used in the study of this problem is given with concentration and time relationships. Special emphasis is placed on studies using P^{32} correlating the technics of radioautography and radioactivity measurement. A unified hypothesis is presented as to the sites of the blood-brain and blood-cerebrospinal fluid barriers as well as the movement of cerebrospinal fluid. The author points out areas for future work in order to obtain a complete understanding of the problem. It is regrettable that some of the recent biochemical studies were not included to give a more complete picture.

This book is of particular interest to neurosurgeons who undertake the diagnosis of brain tumors since the data presented are seemingly quantitative and enable one to observe pathological changes in humans with no detriment to the patient. The discussion of the effect and the underlying principles of cerebrovascular accidents, infections and tumors on ion exchange throughout the central nervous system is excellent and thought provoking.



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Continued from page 1092

Dr. Donald Bickers, Atlanta, has been elected to membership in the Southern Neurosurgical Society.

Drs. Jack C. Norris, Atlanta, Marcus Mashburn, Sr., Cumming, and F. Kells Boland, Jr., Atlanta, have been installed as members of the State Workmen's Compensation Board for a three-year term.

Dr. Walter J. Revell, Louisville, has recently been appointed to the Jefferson County Board of Health.

Dr. Virgil P. Sydenstricker, Augusta, has succeeded Dr. Rufus Payne as dean of postgraduate medical education and professor of medicine at the Medical College of Georgia. Dr. Payne will devote full time to the office of superintendent of the Eugene Talmadge Memorial Hospital.

KENTUCKY

Drs. Louis M. Foltz, Louisville, Gradie Rowntree, Louisville, and Gant Gaither, Hopkinsville, have been appointed by Governor Chandler to a new Kentucky Commission on Alcoholism.

Dr. G. Y. Graves, Bowling Green, Kentucky State Medical Association president in 1953, has been installed as president of the Conference of Presidents and Other Officers of State Medical Associations.

Dr. E. Rudolf Gernert, Louisville, has been presented a plaque in recognition of his five years as president of the Kentucky Tuberculosis Association.

Dr. Reuben N. Lawson, Lawrenceburg, was elected president of the Seventh Councilor District. Dr. Hugh Williams, Carrolton, will serve as vice-president and Dr. Donald Chatham, Shelbyville, has assumed the duties of secretary.

Dr. Beverly Todd Towery has succeeded Dr. J. Murray Kinsman as chairman of the department of medicine at the University of Louisville School of Medicine. Dr. Towery is a graduate of Vanderbilt University School of Medicine and has been associate professor of medicine there since 1953.

Dr. M. A. Bowers, Jr., Louisville, has been named president of the recently organized Kentucky Chapter of Flying Physicians. Drs. Luther Fuller and Homer Martin, also of Louisville, will serve as vice-president and secretary-treasurer respectively.

Dr. W. Winson Pierce, Covington, has received an honorary degree in science from his alma mater, Georgetown College.

The Louisville OB-Gyn Society has named the following officers: Dr. Hugh P. Adkins, president; Dr. Oscar Hayes, vice-president; and Dr. Douglas Haynes, secretary-treasurer.

Dr. Joseph J. Glaboff has assumed the duties of president of the Louisville Pediatric Society. Dr. Selby Love is president-elect and Dr. Fred Pipkin will serve as secretary.

Dr. Harold Bean has joined the staff of the United Mine Workers Hospital at South Williamson.

Dr. Dorothy B. Worcester has resigned after 17 years as head of the baby clinic at the Kenton County Health Department.

Continued on page 52

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Continued from page 50

LOUISIANA

Dr. David F. Bradley, New Orleans, has been elected president of the Louisiana Dermatology Society. Dr. Raphael Ross, Jr., will serve as secretary and treasurer.

Dr. J. William Rosenthal has been honored by the Magazine Lions Club as Lion of the Year.

Dr. Howard Mahorner, clinical professor of surgery at Louisiana State University School of Medicine, has been named president-elect of the Southeastern Surgical Congress, and vice-president of the American Goiter Association.

Dr. V. Medd Hennington, associate clinical professor of dermatology, has been elected to membership in the American Dermatological Association.

Dr. A. J. Walker, associate professor of tropical medicine in the Tulane University School of Medicine, left July 1 for a year in Mexico City as medical parasitologist for the Coordinated Office of the Malaria Eradication Program.

Dr. Oscar Creech, Jr., associate professor of surgery in the College of Medicine at Baylor University, has succeeded Dr. Alton Ochsner as professor and chairman of the department of surgery in the Tulane University School of Medicine.

The Louisiana Group Psychotherapy Society has recently been accepted as an affiliate organization by the American Group Psychotherapy Association. The officers are: Dr. Irwin M. Marcus, president; Dr. Robert Lancaster, president-elect; Dr. Irvin Kraft, treasurer; and Dr. Morton Enelow, corresponding secretary.

Dr. Henry Miles has been elected president of the New Orleans Psychoanalytic Society. Dr. Theodore Watters is the president-elect and Dr. Irwin M. Marcus will serve as secretary-treasurer.

Dr. Vann E. Spruiell, formerly associated with the Tulane University of Louisiana School of Medicine, has been named psychiatrist for the Calasieu Area Guidance Center in Lake Charles.

MARYLAND

Dr. C. Reid Edwards, Baltimore, has been elected president of the Medical and Chirurgical Faculty of the State of Maryland. The other officers are: Drs. S. James T. Marsh, Westminster, Alexander C. Dick, Chestertown, and Richard W. TeLinde, Baltimore, vice-presidents; Dr. Everett S. Diggs, Baltimore, secretary; and Dr. Wetherbee Fort, Baltimore, treasurer.

Dr. William Oliver McLane, Frostburg, has been appointed by the President to review and report on the working plan of the State Fund for Doctors' dependents.

The Maryland Chapter of the American Academy of Pediatrics is establishing two Poison Control Centers. Dr. Samuel Bessman, associate professor of pediatrics, will be in charge of the University of Maryland Hospital and Dr. Thomas E. Reochelderfer, instructor of pediatrics, will head the Johns Hopkins Hospital Center.

MISSOURI

Dr. Harry L. Alexander, St. Louis, has been ap-

pointed to the National Advisory Allergy and Infectious Disease Council.

The Southwestern Bell Telephone Company has named Dr. John W. Berry, St. Louis, general medical advisor.

Dr. Walter Baumgarten, Jr., St. Louis, has been elected president of the Missouri Heart Association.

The Kansas City Society of Ophthalmology and Otolaryngology has installed the following officers: Dr. Barnard C. Trowbridge, president; Dr. William R. Eubank, vice-president; Dr. Dick H. Underwood, secretary; and Dr. James T. Robinson, Jr., treasurer.

The American Board of Obstetrics and Gynecology has certified the following Missouri physicians: Dr. Samuel A. Montello, Kansas City; Dr. Richard I. Muckerman, St. Louis; Dr. Wallace R. Stacey, Independence; and Dr. Charles E. Sutton, Cape Girardeau.

Dr. Albert Preston, Jr., Kansas City, has been presented a medal by Bishop Edward R. Welles in recognition of his contributive work in the Episcopal Church.

Dr. Joseph E. Flynn, Columbia, has been elected president of the Missouri Society of Pathologists.

Dr. Paul Hines, Kansas City, has been named president-elect of the National Association of Private Psychiatric Hospitals.

The Missouri chapter of the American College of

Continued on page 59

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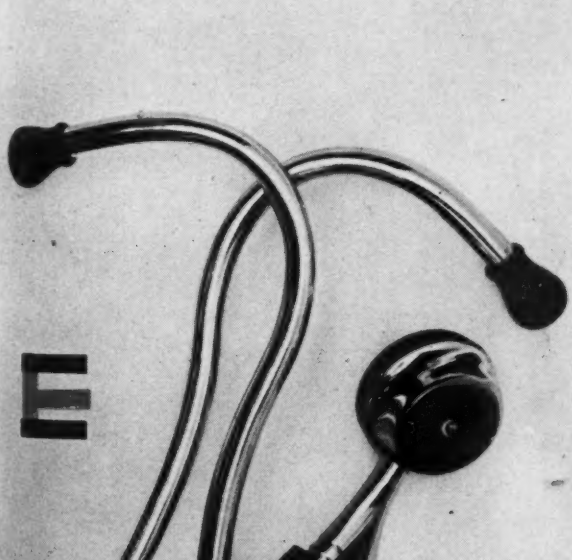

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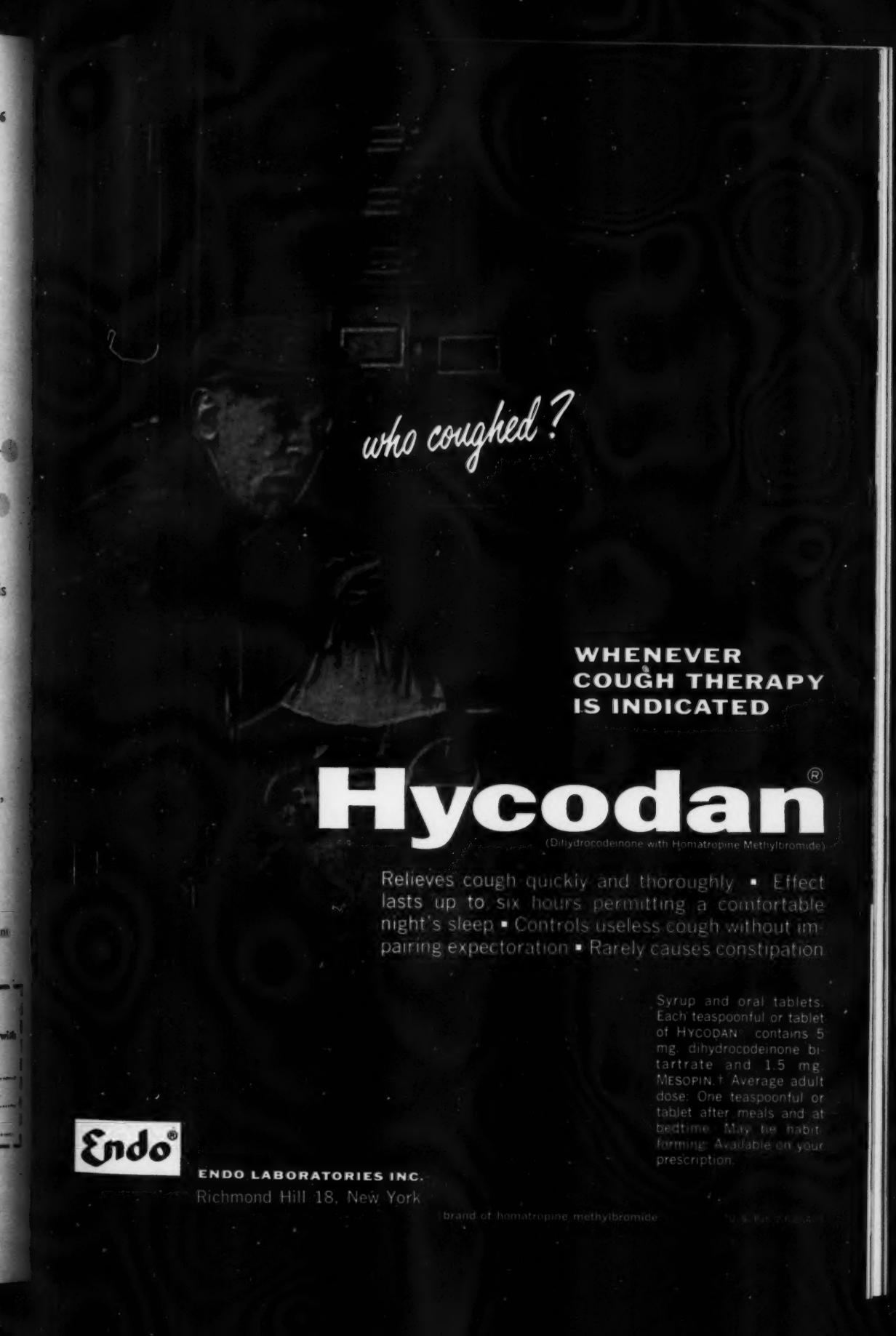

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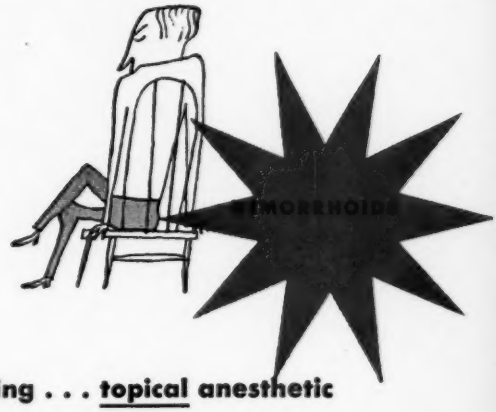

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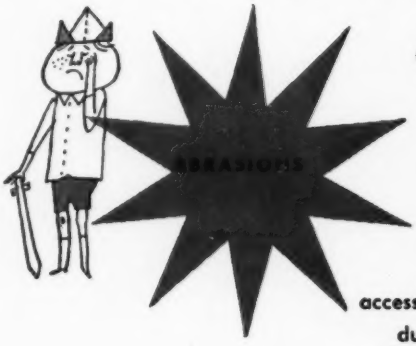

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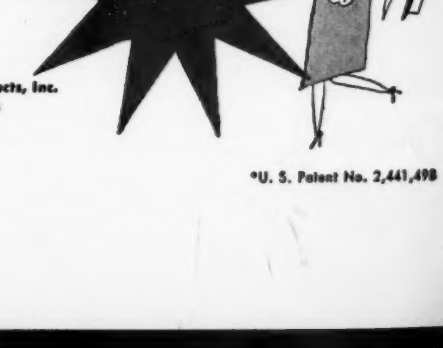

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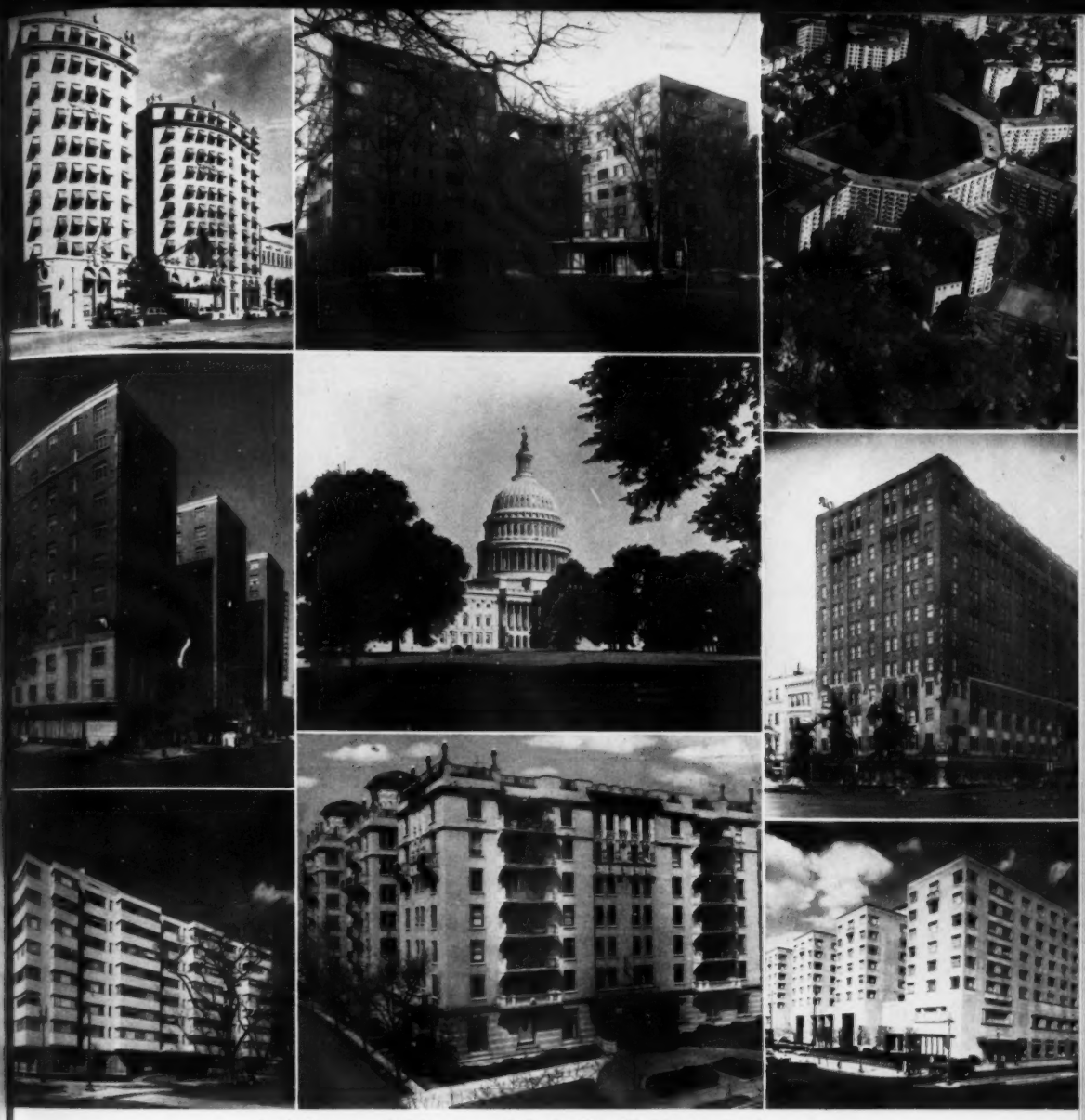

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November 12-15, 1956

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Arrival Date.....	.....hour.....a.m.....p.m.
Departure Date.....	.....hour.....a.m.....p.m.

THE NAME OF EACH HOTEL GUEST MUST BE LISTED. Include the names of all persons for whom you are requesting reservations and who will occupy the room (s):

Name of Occupant (s)	Address
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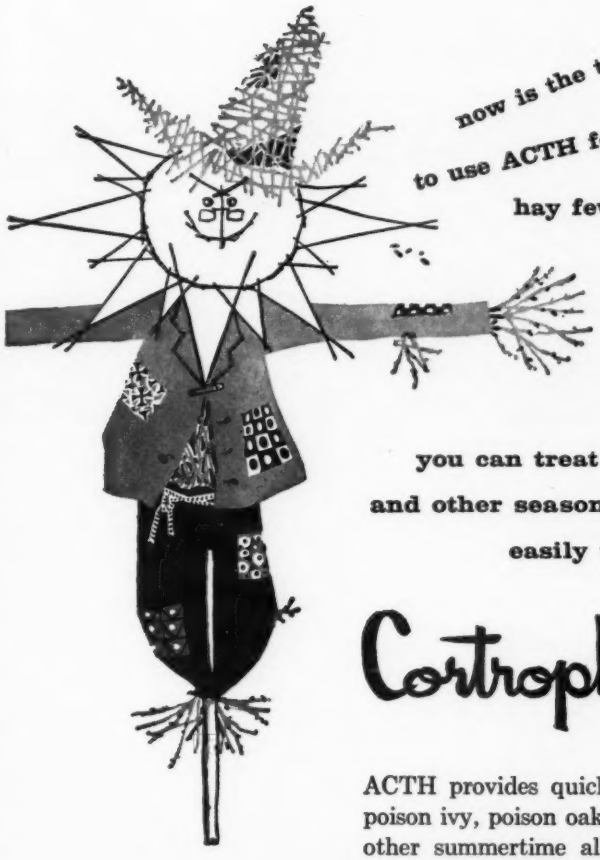
If the hotels of your choice are unable to accept your reservation, the Housing Bureau will make as good a reservation as possible elsewhere.



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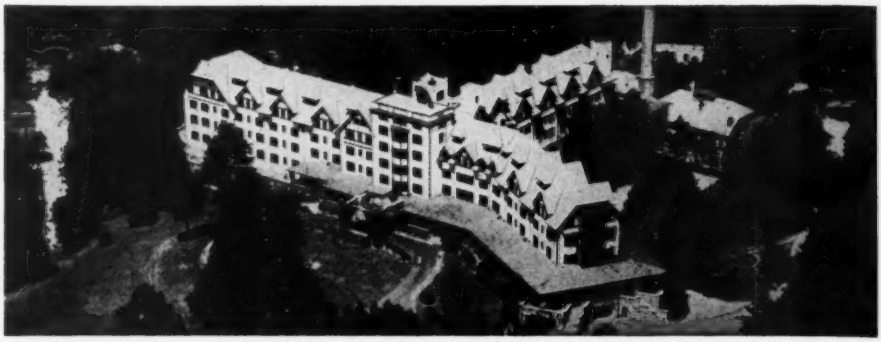

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ORANGE NEW JERSEY

Continued from page 53

Surgeons has elected the following officers: Dr. John J. Modlin, Columbia, president; Dr. W. A. Bloom, Fayette, vice-president; and Dr. James M. Baker, Columbia, secretary-treasurer.

Dr. Louis Berard has been elected president of the St. Louis Urological Society. Dr. Robert F. Hickey is president-elect and Dr. J. Byron Beare will serve as secretary-treasurer.

Dr. Ira H. Lockwood, Kansas City, has been awarded an honorary Doctor of Science degree by Buena Vista College, Storm Lake, Iowa.

Dr. J. T. Leslie, Jefferson City, was presented a gold watch and plaque by the Cole County Medical Society in recognition of his fifty years in the practice of medicine.

Drs. R. M. Norman and J. L. Gentry were honored by the Ava Kiwanis Club for their fifty years of service in the practice of medicine.

The following physicians have been certified by the American College of Chest Physicians: Dr. Florence E. MacInnis, Kansas City; Drs. John B. Meyers, Masao Ōhmoto, and R. Jerome Williams, St. Louis. Dr. Alfred Goldman, St. Louis, was re-elected regent of the College for several states. Dr. Charles A. Brasher, Mount Vernon, is governor for Missouri.

Dr. Edwin C. Ernst, St. Louis, was presented an honorary degree of Doctor of Humane Letters by Moravian College, Bethlehem, Pennsylvania.

The Scott County Chapter of the National Foundation for Infantile Paralysis has presented Dr. W. O. Finney, Chaffee, a certificate of appreciation and 15 year pin.

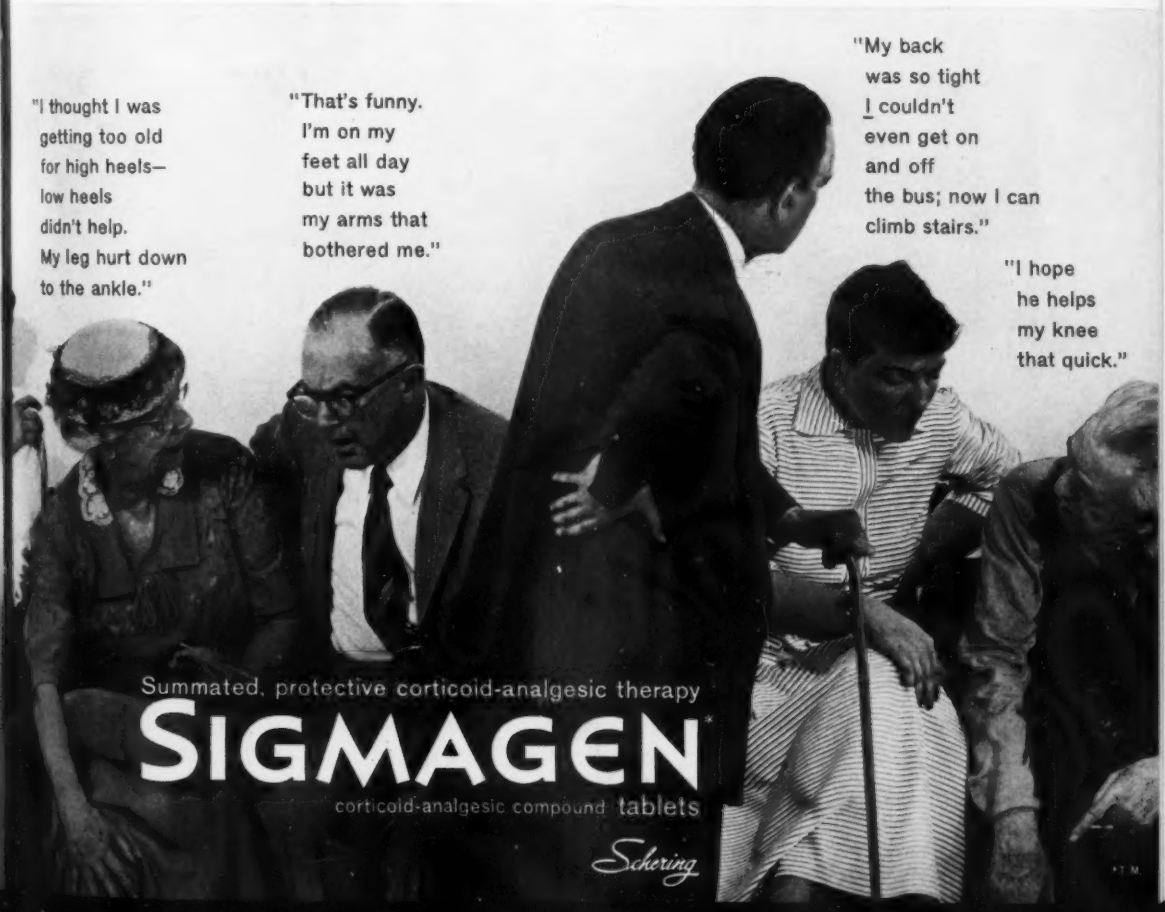
The College Medal of the American College of Chest Physicians has been awarded to Dr. Henry C. Sweany, Mount Vernon, for meritorious achievement in the specialty of diseases of the chest.

Dr. John Wood Williams, Springfield, has been presented the W. Scott Johnson annual award of the Missouri Public Health Association in recognition of his long service to public health in Missouri.

Dr. Joseph E. Flynn, professor and chairman of the department of pathology of the University of Missouri has been named president-elect of the Missouri Society of Pathologists.

The following appointments have been made by the University of Missouri School of Medicine: Dr. Theodore E. Keats, associate professor of radiology; Dr. Jack M. Artt, assistant professor of medicine; Dr. Jacob S. Roden, assistant professor of obstetrics and gynecology; Dr. Helen M. Waiches, instructor in pediatrics; Drs. Mary Elizabeth Bowen, Marie Jabbar, and Carlos P. Trevino, assistant instructors in pediatrics; Drs. James Frederick Ransdell and Bonita

Conitnued on page 67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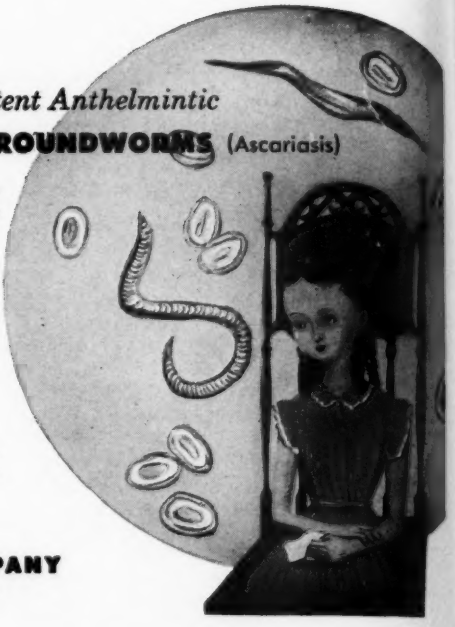

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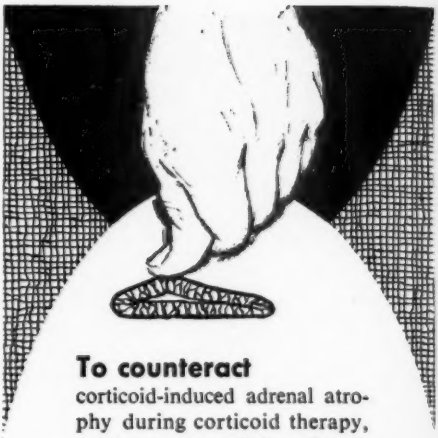

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TENNESSEE VALLEY MEDICAL ASSEMBLY

Sponsored by the Chattanooga and Hamilton County Medical Society

The Read House, Chattanooga, Tennessee

Monday, October 1, and Tuesday, October 2, 1956

Monday, 7:30-9:00 a.m.

Registration

Monday, 9:00 a.m. to 12:00 noon

WALTER C. ALVAREZ, M.D., Chicago, Illinois, "New Observations on Little Strokes."

PHILIP S. HENCH, M.D., Mayo Clinic, Rochester, Minn., "The Treatment of Rheumatoid Arthritis."

J. P. GREENHILL, M.D., Chicago, Illinois, "What's New in Obstetrics."

GUY W. HORSLEY, M.D., Richmond, Virginia, "Carcinoma of the Colon and Rectum."

DWIGHT H. MURRAY, M.D., President of the American Medical Assn., Napa, Calif., "The Role of the A.M.A. in Improving and Increasing Scientific Programs Throughout the Country."

Monday, 2:00 to 5:00 p.m.

EUGENE P. PENDERGRASS, M.D., University of Pennsylvania, Philadelphia, Penn., "The Responsibility of the General Practitioner and the Radiologist in the Diagnosis of Curable Cancer of the Lung."

TOM D. SPIES, M.D., Nutrition Clinic, Birmingham, Alabama, "The Recent Advances in the Treatment of Nutritional Disorders."

FRANCIS EUGENE SENEAR, M.D., Chicago, Illinois, "The Diagnosis and Treatment of the Bullous Dermatoses."

JAMES L. POPPEN, M.D., The Lahey Clinic, Boston, Mass., "Indications for Sympathectomy."

Question and Answer Period, GUY W. HORSLEY, M.D., Moderator .

Monday, 7:00 p.m.

Banquet. Speaker: FRED C. SCHWARZ, M.D., Sydney, Australia, "Diagnosis, Prognosis and Treatment of Communism."

Tuesday, 9:00 a.m. to 12:00 noon

HENRY W. CAVE, M.D., New York, N. Y., "Ulcerative Colitis."

RUSSELL BLATTNER, M.D., Baylor University College of Medicine, Houston, Texas, "Encephalitis."

J. HARTWELL HARRISON, M.D., Peter Bent Brigham Hospital, Boston, Mass., "Clinical States Due to Abnormal Adrenocortical Function."

HENRY L. BOCKUS, M.D., Philadelphia, Penn., "Functional Disorders of the Digestive Tract."

ROBERT E. GROSS, M.D., Boston, Mass., "Surgical Treatment for Interauricular Septal Defects."

Tuesday, 2:00 to 5:00 p.m.

JOHN S. LUNDY, M.D., Mayo Clinic, Rochester, Minn., "Pain Relief."

T. CAMPBELL THOMPSON, M.D., New York, N. Y., "Orthopedic Conditions of Special Interest to the Pediatrician and General Practitioner."

HENRY L. BOCKUS, M.D., Philadelphia, Penn., "The Acute Abdomen."

MICHAEL DeBAKEY, M.D., Houston, Texas, "Surgical Treatment of Diseases of the Aorta."

Question and Answer Period, HENRY W. CAVE, M.D., Moderator.

For hotel reservation write **Chattanooga Convention and Visitors Bureau, 119 Broad Street, Chattanooga, Tennessee,** indicating whether a hotel or a motel is desired, whether a single or double room and if double room whether double bed or twin beds and giving the anticipated time of arrival in Chattanooga.

IMPORTANT NOTICE—The Southern Medical Association will have a Golden Anniversary Celebration at The Read House in Chattanooga following the close of the Tennessee Valley Medical Assembly program, the first activity of the Celebration to be a dinner meeting on Tuesday evening, October 2, with a closing session Wednesday forenoon. The Celebration program will be historical, informative and inspirational. The Southern Medical Association was born in Chattanooga on October 2-3, 1906. Physicians attending the Assembly are cordially invited to remain over for the Southern Medical Association Golden Anniversary Celebration.

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1. Danko, C. W., Buni, D., and Bergendal, D. M.: Am. Pract. & Digest Treat. 6:1055, 1955.
2. Holbrook, W. P.: M. Clin. North America 39:405, 1955.
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W. E. Wilkinson, M.D.

Harlan Mental Health Center
Harlan, Ky.
C. H. Crudden, M.D.

Continued from page 59

Jeanne Peterson, assistant instructors in pathology; Drs. Kenneth Glover, Wyeth Hamlin, Doyle C. McCraw, Peter V. Siegel, Arch E. Spelman and James H. Trolinger, Preceptor in General Practice.

The faculty promotions in the University of Missouri School of Medicine include the following: Dr. Stuart O. Landry, from instructor to assistant professor of anatomy; Dr. F. Eugene Doenges, from assistant instructor to instructor; Dr. Constantine S. Anast, from instructor to assistant professor in pediatrics; Dr. Clement E. Brooke, from instructor to assistant professor in pediatrics; and Dr. Fredric E. Simpson, from instructor to assistant professor in pediatrics. Dr. Simpson has also been appointed Medical Director of the Missouri State Crippled Children's Service.

NORTH CAROLINA

Dr. C. D. Eatman, Rocky Mount, has been named president-elect of the North Carolina Tuberculosis Association.

The officers of the newly organized North Carolina Chapter of the American College of Surgeons are: Dr. William Sprunt, Winston-Salem, president; Dr. George Wood, High Point, vice-president and president-elect; and Dr. Alexander Webb, Jr., Raleigh, secretary-treasurer. The Councilors are Drs. Howard Bradshaw, Winston-Salem; Edwin Alyea, Durham; William Farmer, Fayetteville; James Marshall, Winston-Salem; and Russell Lyday, Greensboro.

Dr. George C. Ham, professor and chairman of the department of psychiatry of the University of North Carolina School of Medicine, has been named to membership on the Committee of Psychiatry of the Division of Medical Science, National Research Council of the National Academy of Sciences. He has also been appointed to serve on the Selection Committee for Senior Research Fellowships of the National Institutes of Health.

Dr. Walter R. Benson has joined the staff of the University of North Carolina School of Medicine as assistant professor in the department of pathology.

OKLAHOMA

Dr. Arthur Buswell, Hennessey, has been named chief-of-staff at the Kingfisher community hospital.

Dr. Lucien M. Pascucci, Tulsa, has been elected president of the Oklahoma State Radiological Association. The vice-president and secretary-treasurer, also of Tulsa, are Drs. Simon Pollack and Sol Wilner, respectively.

Dr. William S. Crawford, Tulsa, has retired after 26 years as medical director of the Carter Oil Company. He will be succeeded by Dr. Tom Hall Mitchell, Tulsa, who has been assistant director since 1938.

SOUTH CAROLINA

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Continued on page 68

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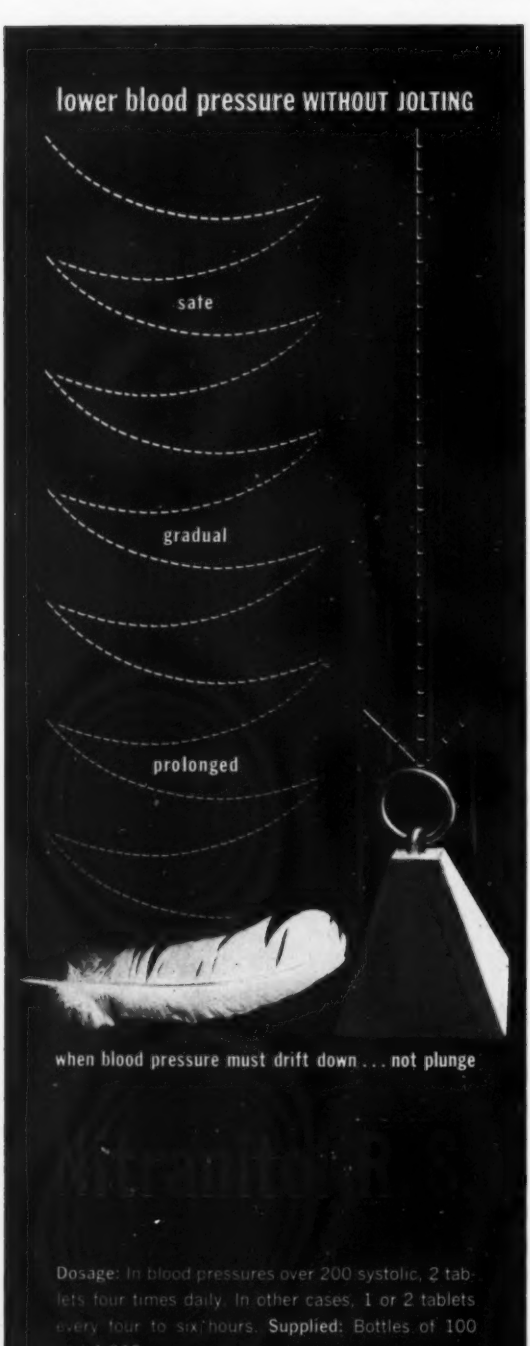
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Continued from page 67

W. A. Smith was awarded an honorary degree of LLD by the Citadel.

Dr. Richard Sosnowski has been certified by the Board of Obstetrics and Gynecology.

TENNESSEE

Dr. Robert W. Quinn, Nashville, has been named president-elect of the Middle Tennessee Heart Association. Dr. Laurence A. Crossman, Nashville, has been installed as president. The new directors, all of Nashville, are Drs. George Brothers, Douglas Riddell, James J. Callaway, and Rudolph A. Light.

Dr. James W. Hall, Trenton, has been elected president of the medical staff of St. Mary's Hospital, Humboldt. Drs. John Jackson, Dyer, and Harold G. Barker, Humboldt, are the other officers.

Dr. Denton Norris, Livingston, was appointed county chairman of the American Cancer Society Crusade.

Dr. Harold H. Fry, Paris, has become associated with the staff of Nobles Hospital.

Dr. Chester K. Jones, Jackson, has been named president of the Tennessee Society of Pathology.

Dr. William E. Allison, Nashville, has been appointed medical director of the Nashville Regional Blood Center.

Dr. P. D. Jones, Milan, will serve as president of the staff of Milan Hospital. Dr. James O. Fields is vice-president, and Dr. P. G. Williams, secretary.

Dr. Carl C. Gardner, Jr., Columbia, has been elected president of the Maury County Tuberculosis Association.

Dr. Ira L. Arnold, Chattanooga, has assumed the duties of vice-president of the Tennessee Academy of Ophthalmology and Otolaryngology.

Dr. Herbert C. Francis, Nashville, has been appointed councilor to the American College of Radiology for Tennessee. Dr. Walter Hankins, Johnson City, is the alternate councilor.

Dr. Freeman C. Hays, Chattanooga, has become associated with the Brainerd Clinic.

A Children's Convulsive Seizure Clinic has been opened by the University of Tennessee College of Medicine in the Pediatric Clinic of the John Gaston Hospital. Dr. James G. Hughes, professor of pediatrics, will serve as director.

TEXAS

Dr. B. Dixon Holland, Denton, has been named secretary of the AMA Council on Industrial Health by the American Medical Association Board of Trustees.

Dr. Robert Butler is the new president of the Childress Lions Club.

Drs. James N. Walker and Abe Greines have been elected to the Fort Worth Board of Education.

The American College of Chest Physicians has inducted the following Texas physicians into fellowship: Drs. Kleberg Eckhardt, Corpus Christi; B. B. Elster, Port Arthur; Robert B. Giles, Dallas; O. B.

Gober, Temple; Andrew B. Goesl, Texarkana; William F. Miller, Dallas; Philip M. Prieto, El Paso; Paul Richburg, Dallas; Fred D. Spencer, Jr., Brownwood; and James B. Stubbs, Galveston.

The following Texans have been certified by the American Board of Obstetrics and Gynecology: Drs. Wayne F. Baden, Raymondville; Robert G. Campbell, Ben K. Howard, Hugh D. Murray, Asa A. Newsom, Jr., Harold R. Thomas, and Joseph E. Wilke, Jr., all of Dallas; James W. Carter, Jr., and William E. Strozier, San Antonio; Harry W. Demarest and Kenneth S. Kurita, El Paso; Julius L. Jinkins, Jr., Galveston; Otto F. Schoenvogel, Jr., and Alvin S. Wexler, Houston; Masamichi Suzuki, Sheppard Air Force Base; and George W. Wyatt, Amarillo.

Dr. Bruce Terrill has been named president of the Stephenville Junior Chamber of Commerce.

Dr. Fred W. Taylor, Wichita Falls, has become a Diplomate of the American Board of Urology.

VIRGINIA

Dr. Mallary S. Andrews has been installed as president of the Norfolk County Medical Society. The other officers are: Dr. J. Franklin Waddill, president-elect; Dr. W. C. Salley, vice-president; Dr. John S. Thiemeyer, Jr., recording secretary; Dr. Robert B. Gahagan, treasurer; Dr. Bernard Lidman, parliamentarian; and Dr. M. Kirwan King, local counsellor.

The Alexandria Medical Society has elected the following new officers: Dr. Haskins H. Ferrell, Jr., president; Dr. Eugene R. Grether, president-elect; Dr. James M. Moss, vice-president; Dr. Jean Lockhart, secretary; and Dr. Robert H. Anderson, treasurer. Drs. Richard E. Palmer, Christopher J. Murphy, Jr., and F. Preston Titus were appointed to the Executive Committee.

Dr. Harry B. Stone, Jr., has been installed as president of the Roanoke Academy of Medicine. Drs. Alexander McCausland and George Bourne are the new vice-presidents and Dr. Louis Ripley will serve as secretary-treasurer. Dr. David S. Garner was elected president-elect.

Dr. Joseph D. Collins, dean of Portsmouth surgeons, has been honored by the members of the medical staff of King's Daughters' Hospital in recognition of fifty-one years of service in the practice of medicine.

Dr. Charles W. Whitmore, Lynchburg, was appointed medical director for the recently organized First Colony Life Insurance Company.

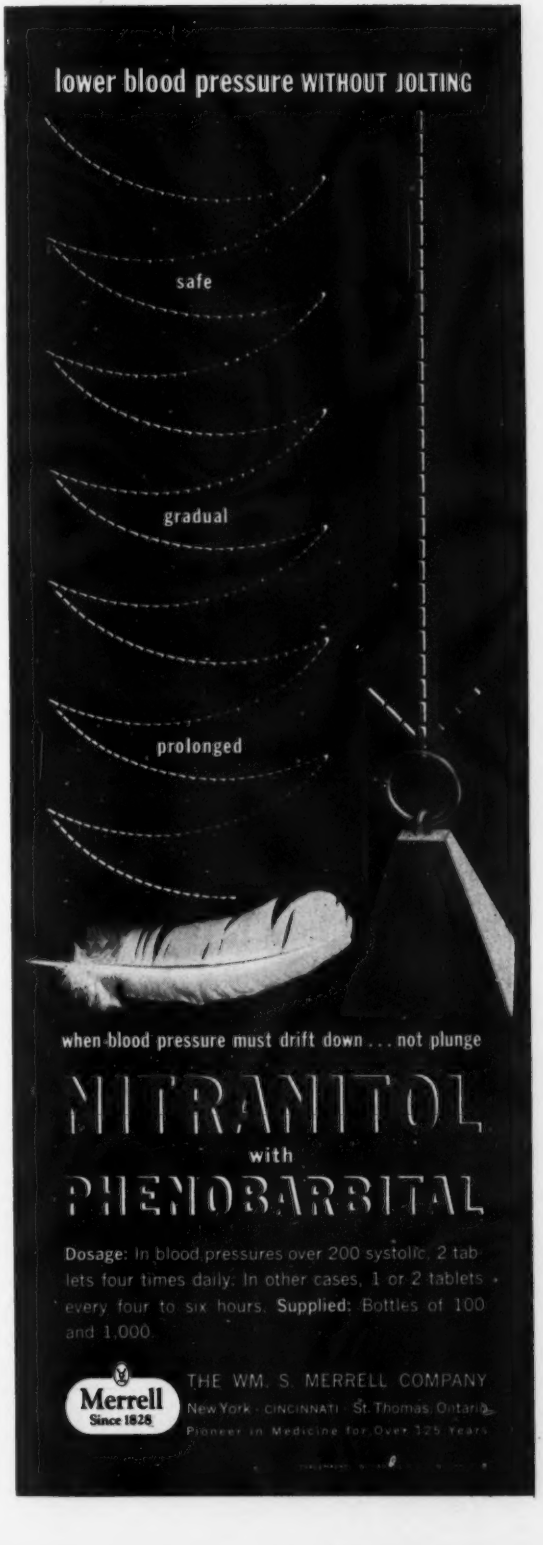
Dr. Kenneth N. Payne has assumed the duties of superintendent of Pine Camp Hospital in Richmond.

Dr. R. Blackwell Smith, Jr., has succeeded Dr. William T. Sanger as president of the Medical College of Virginia. Dr. Sanger, who had been president of the college for thirty-one years, became chancellor.

Dr. David M. Hume, formerly assistant professor of surgery and director of surgical research at the Harvard Medical School has assumed his duties as professor of surgery at the Medical College of Virginia.

Dr. Warren E. Weaver has succeeded Dr. R. Blackwell Smith, Jr., as dean of the school of pharmacy.

Continued on page 75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Infectious Diseases in Pediatrics	February 4-9, 1957
Surgery of the Hand	March 21-23, 1957
Industrial Medicine	April 4 and 5, 1957
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Cream 0.5%

with METICORTELONE, original brand of prednisolone

- more active than topical hydrocortisone, milligram for milligram
- no edema and sodium retention reported upon topical administration
- provides topical METICORTELONE in the free alcohol form. For effective relief of allergic (atopic) dermatoses, poison ivy dermatitis and other contact dermatoses, nonspecific anogenital pruritus.

formula: Each gram of METI-DERM Cream contains 5 mg. of prednisolone, free alcohol, in a water-washable base.

also for allergic, inflammatory dermatoses, minor secondary infections

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formula: Each gram contains 5 mg. prednisolone and 5 mg. neomycin sulfate (equivalent to 3.5 mg. neomycin base) in a white petrolatum base.

packaging: METI-DERM Cream, 10 Gm. tube.
METI-DERM Ointment, 10 Gm. tube.

METI-DERM,* brand of prednisolone topical.
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TABLETS *(yellow, coated), each containing 50 mg. Trasentine® hydrochloride (adiphenine hydrochloride CIBA) and 20 mg. phenobarbital.*

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Summit, N. J.

Continued from page 69

WEST VIRGINIA

Dr. Walter E. Vest, Huntington, was elected to membership on the Council on Constitution and By-Laws of the American Medical Association.

Dr. Karl E. Weier, Bluefield, was among the top ten winners in the 1956 international Graflex Photo Contest.

Dr. Bruce H. Pollock, director of the Cabell-Huntington Health Department, has been elected first vice-president of the West Virginia Public Health Association.

Dr. Carrell M. Caudill, Charleston, has been certified by the American Board of Neurological Surgery.

Six physicians have been elected to membership on the county school boards: Dr. E. Burl Randolph, Clarksburg, Harrison County; Dr. William P. Bradford, Moundsville, Marshall County; Dr. A. B. Carr, War, McDowell County; Dr. J. W. Stokes, Hinton, Summers County; Dr. Richard F. Miller, Paden City, Wetzel County; and Dr. Paul L. McCuskey, Parkersburg, Wood County.

Dr. Edward H. Hunter, formerly of Webster Springs, has become associated with the McClung Hosiptal at Richwood.

Drs. John T. Chambers, Charleston, and Charles S. Harrison, Clarksburg, have been certified by the American Board of Obstetrics and Gynecology.

Dr. William J. Kopp, Huntington, was recently certified by the American Board of Pediatrics.

Dr. Robert D. Woodward, Elkins, head of the department of psychiatry at the Golden Clinic, has been named an associate member in the American Psychiatric Association.

Dr. John Bankhead Banks, Charleston, has assumed the duties of president of the University of Virginia Medical Alumni Association.

Dr. Robert D. Crooks, Parkersburg, has been elected a fellow in the American Academy of Pediatrics.

Dr. Max Koenigsberg, Charleston, has been named to fellowship in the American College of Cardiology.

Dr. Guy H. Michael, Jr., Parsons, has been elected president of the Barbour-Randolph-Tucker Medical Society. The other officers are: Dr. John E. Lenox, Philippi, first vice-president; Dr. Paul D. Snedegar, Philippi, second vice-president; Dr. A. C. Thompson, Elkins, secretary; and Dr. Robert R. Rector, Elkins, treasurer.

The Fort Henry Academy of Medicine has named the following officers: Dr. Charles H. Hiles, Wheeling, president; and Dr. Thomas L. Thomas, Wheeling, secretary-treasurer.

Dr. R. M. Sonneborn has been elected president of the Ohio County Medical Society. Dr. Francis J. Gaydosh is vice-president and Dr. Joseph L. Curry is secretary. Dr. A. J. Niehaus was re-elected treasurer.

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"I don't know about bathtubs, but two days ago I couldn't reach a shelf higher than that."

"I thought maybe I slept in a draft. Never had a stiff neck like this before."

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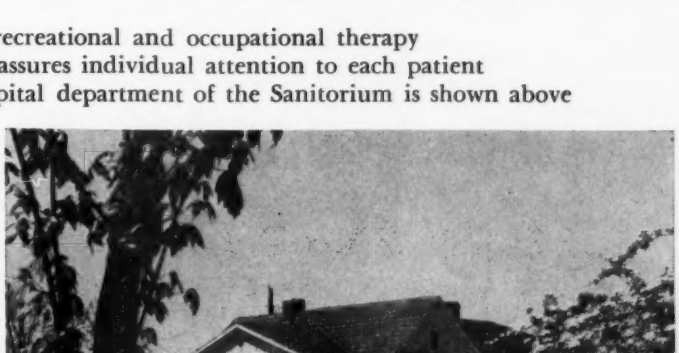

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Reference: 1. Pocock, D. G.: Personal communication.

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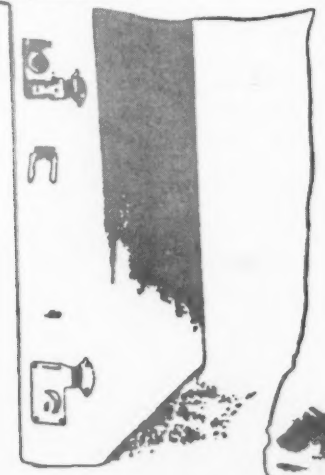

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